From THE DEPARTMENT OF MOLECULAR MEDICINE
AND SURGERY
Karolinska Institutet, Stockholm, Sweden

THROMBOLYSIS IN VASCULAR SURGERY

Linn Smith

Karolinska Institutet

Stockholm 2015

Cover illustration depicts the molecular structure of rt-PA; drawing by the author.
All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Printed by Eprint AB 2015.

ISBN 978-91-7676-165-6

Institutionen för Molekylärmedicin och Kirurgi

Thrombolysis in Vascular Surgery

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Thoraxaulan, Thoraxhuset, Karolinska Universitetssjukhuset Solna

Fredagen den 11 december 2015 kl 09.00

av

Linn Smith, leg. läkare

Huvudhandledare:
Docent Carl-Magnus Wahlgren, MD, PhD
Karolinska Institutet
Institutionen för Molekylärmedicin och Kirurgi
Enheten för Kärlkirurgi

Bihandledare:
Professor Eric Wahlberg
Linköpings Universtitet
Institutionen för Medicin och Hälsa
Enheten för kardiovaskulär medicin

Docent Gun Jörneskog
Karolinska Institutet
Institutionen för Kliniska Vetenskaper
Enheten för kardiovaskulär medicin

Opponent:
Professor Lars Lönn
Köpenhamns Universitet
Institutet för Klinisk Medicin

Betygsnämnd:
Docent Margareta Holmström
Karolinska Institutet
Institutionen för Medicin, Solna
Enheten för internmedicin

Docent Loghman Henareh
Karolinska Institutet
Institutionen för Medicin Huddinge
Enheten för kardiologi

Docent Gunnar Plate
Lunds Universitet
Medicinska fakulteten

Per Aspera Ad Astra

ABSTRACT

Background and aims:
Thrombolysis is in common use in the treatment of acute forms of vascular disease. It may be used both systemically and locally, in the latter case through an endovascular approach, so-called catheter-directed thrombolysis.
The aims of this thesis were to investigate how thrombolysis affects performance-related outcomes pertaining to vascular patency after thrombolysis, and how it affects patient safety and the development of complications.
Methods: Retrospective reviews of patient medical records (all studies) and of data collected from the national stroke and vascular surgery registries (Study II). Study I investigated the outcomes of thrombolysis after infrainguinal bypass graft occlusion in 123 consecutive patients. In Study II, the safety-related outcomes after carotid endarterectomy and stenting (CEA and CAS) were evaluated in 79 patients having undergone systemic thrombolysis for stroke, and this cohort was compared with the 3,998 patients treated by the same methods but without preceding thrombolysis. In Study III, 149 episodes of dialysis access occlusion treated by open surgery or thrombolysis were investigated concerning patency and risks of rethrombosis. Study IV assessed the influence of patient level of care during catheter-directed thrombolysis for limb ischaemia and dialysis access thrombosis on safety-related outcomes, and investigated possible risk factors for patient transfer to a higher level of care.
Results:
In **Study I,** technical success of CDT was achieved in 85% of cases with an amputation-free survival of 89% and 75% at one and 12 months. Higher age and acute critical limb ischaemia were adversely associated with amputation-free survival. Synthetic grafts had a tendency toward reduced amputation-free survival. **Study II** showed a similar stroke and death rate following CEA/CAS for patients having undergone systemic thrombolysis compared with those who had not (2.5% versus 3.8%, P=0.55). There was no significant increase in bleeding complications in the thrombolysis cohort (3.8% versus 3.3%, P=0.79). In **Study III**, CDT of native and prosthetic dialysis accesses yielded a decreased risk of rethrombosis (HR 0.41; 95% CI 0.04-0.98) and native fistulas exhibited better patency both after CDT and open surgery. The complication rate was 2.7% (infection only; there was no death, stroke, severe bleeding or myocardial infarction). **Study IV** showed no differences in the rate of complications (including major bleeding, myocardial infarction and stroke) in patients on the general vascular ward compared with those under a higher level of care on the postoperative recovery unit. Cardiac disease was an independent risk factor for patient transfer to a higher level of care.
Conclusions:
CDT yields good results in terms of technical success and amputation-free survival both in the short and medium term after treatment of infrainguinal bypass graft occlusion. Prior systemic thrombolysis seems not to increase the periprocedural risk of CEA or CAS in patients with symptomatic carotid artery stenosis. CDT reduces the risk of rethrombosis both for native and prosthetic fistulas after access thrombosis even after accounting for adjunctive procedures (undertaken more frequently in those undergoing CDT). Care on a general vascular ward appears safe in the context of CDT. Nonetheless, preexisting cardiac disease was shown to increase the risk of transfer and highlights the importance of appropriate patient selection.
Thrombolysis is associated with safe and efficaceous treatment of many groups of vascular surgical patients. However, continuous evaluation of outcomes is required in view of the rapid development of endovascular techniques and devices, and further work should also be done on medical adjunctive management in order to maximise vascular patency after successful thrombolysis.

LIST OF SCIENTIFIC PAPERS

I. **Thrombolysis for lower extremity bypass graft occlusion**
Linn Koraen, Monica Kuoppala, Stefan Acosta and Carl-Magnus Wahlgren
Journal of Vascular Surgery 2011;54;1339-44

II. **Urgent carotid surgery and stenting may be safe after systemic thrombolysis for stroke**
Linn Koraen-Smith, Tomas Troëng, Martin Björck, Björn Kragsterman and Carl-Magnus Wahlgren
Stroke 2014;45;776-80

III. **Outcomes of surgical thrombectomy and thrombolysis for dialysis access thrombosis**
Linn Koraen-Smith, Mateusz Krasun, Matteo Bottai, Ulf Hedin and Carl-Magnus Wahlgren
Submitted

IV. **Influence of the level of care on the safety of intra-arterial catheter directed thrombolysis**
Linn Koraen-Smith, Margaretha Wängberg, Carl Montán, Peter Gillgren and Carl-Magnus Wahlgren
Submitted

CONTENTS

LIST OF ABBREVIATIONS

AHA	American Heart Association
AMI	Acute myocardial infarction
APTT	Activated partial thromboplastin time
ASA	American Stroke Association
AVF	Arterio-venous fistula
AVG	Arterio-venous graft
CABG	Coronary artery bypass grafting
CAS	Carotid artery stenting
CDT	Catheter-directed thrombolysis
CEA	Carotid endarterectomy
CI	Confidence interval
CT	Computed tomography
CVC	Central venous catheter
DM	Diabetes mellitus
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ESRF	End-stage renal failure
GI	Gastro-intestinal
Gp	Glycoprotein
GUSTO	Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries
HD	Haemodialysis
HR	Hazard ratio
INR	International Normalised Ratio
IVT	Intravenous thrombolysis
LMWH	Low molecular weight heparin
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio

PACS	Picture archiving and communication system
PAI-I	Plasminogen activator-inhibitor I
PE	Pulmonary embolism
PMT	Pharmacomechanical thrombolysis
PT	Partial thromboplastin time
ROTEM	Rotational thromboelastometry
RR	Relative risk
RT	Rheolytic thrombectomy
rt-PA	Recombinant tissue plasminogen activator
SK	Streptokinase
STILE	Surgery versus Thrombolysis for Ischemia of the Lower Extremity
TEG	Thromboelastography
TF	Tissue factor
TIA	Transient ischaemic attack
TNK-t-PA	Tenecteplase
TOPAS	Thrombolysis Or Peripheral Arterial Surgery
TOS	Thoracic outlet syndrome
t-PA	Tissue plasminogen activator
UK	Urokinase
u-PA	Urokinase-type plasminogen activator

1 INTRODUCTION

1.1 BACKGROUND

Thrombolysis (from the Greek words *thrombos*, meaning lump or clot, and *lysis*, meaning loosening) is the process whereby a blood clot is dissolved through the enzymatic degradation of the fibrin mesh that provides it with its structural stability. Today, the term is generally used to describe the pharmacological induction of clot lysis for the treatment of vascular embolism or thrombosis.

Thrombolysis has been in clinical use since the 1940s, when Garner and Tillett[1] published the first work detailing the effect of injecting streptokinase (SK), a thrombolytic substance, into the thick, liquefied pleural effusions of patients with empyema. Since then, the intravenous administration of thrombolytics, so-called systemic thrombolysis, has been used for the treatment of both myocardial infarction (AMI) and stroke. However, systemic thrombolysis is, as the name suggests, non-specific in terms of drug delivery and alternative methods have subsequently been developed to increase therapeutic precision and reduce the risk of unwanted side-effects.

In 1974, Dotter and colleagues described for the first time the placement of an intra-arterial catheter for the selective, continuous deposition of SK into the occluded target vessel in the treatment of 17 patients with lower extremity thrombo-embolism.[2] In this very early series of what is now known as catheter-directed thrombolysis (CDT), clot lysis (as confirmed by angiography) was achieved in 12 of 17 cases. Subsequently, there has been significant development of both thrombolytic drugs and endovascular techniques[3], which has led to a steady increase in the use of CDT, in particular in the treatment of lower limb ischaemia.

Today, CDT is used by vascular surgeons, interventional cardiologists, neuroradiologists and interventional radiologists in the treatment of all forms of vascular disease.

1.2 THROMBOLYSIS THROMBOLYTICS

1.2.1 Thrombosis and embolism

The acute occlusion of a blood vessel due to clot formation can have devastating physiological consequences. Time is of the essence in order to minimise tissue ischaemia and thus minimise tissue damage or loss. Atraumatic vessel occlusion may be a result either of transportation of a preformed thrombus (e.g. from the heart) that commonly lodges at a junction or a site of narrowing in the vessel, leading to its occlusion (known as embolisation), or it may be due to thrombus formation secondary to the rupture of an atherosclerotic plaque, which causes platelet adhesion, activation of the clotting cascade and, eventually, the formation of a clot (known as thrombosis).

The formation of a thrombus is initiated by platelet activation through exposure of subendothelial collagen, which causes glycoproteins (GPIb, IV, V, IX) on the platelet surface to interact directly with the collagen; through collagen-bound von Willebrand factor, leading to platelet adhesion and activation; or through direct activation of platelets through tissue factor (TF). Through interactions with factors VIIa and factor IX, this pathway leads to the generation of thrombin and thereby activation of platelets[4] and conversion of fibrinogen to fibrin monomers. These monomers then polymerise into a stable matrix that provides the thrombus with a scaffold.[5] The fibrin content of a thrombus appears to be correlated to ischaemic time[6], which suggests that time is a variable affecting the stability and structure of the fibrin matrix.

1.2.2 Fibrinolysis

In vivo, the breakdown of fibrin is activated by endogenously produced tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). These are produced mainly by endothelial cells, and their activity is strictly regulated by inhibitors of plasminogen activators such as plasminogen activator inhibitor-1 (PAI-1) and by direct plasmin inhibitors (such as α1-antiplasmin and α2-macroglobulin).[7] In vivo, fibrinolysis is therefore a very localised and highly regulated process. t-PA binds to fibrin, which leads to a conversion of fibrin-bound plasminogen to plasmin. The action of t-PA is therefore relatively clot-specific. *Figure 1* shows a schematic outline of the process.

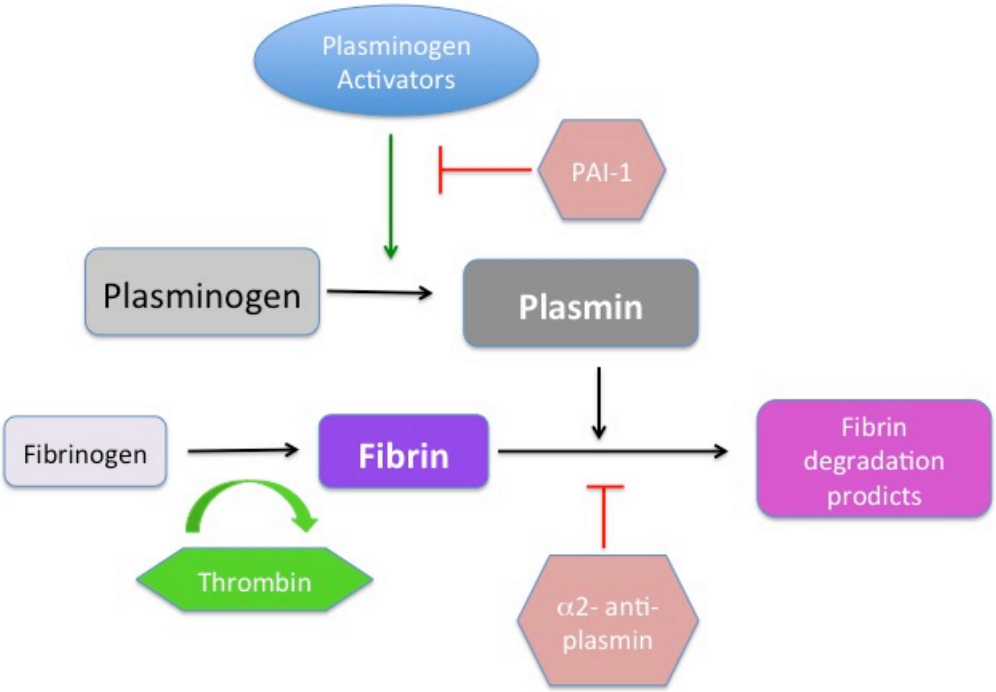

Figure 1: *Schematic representation of the fibrinolytic process (adapted from Banerjee et al.[8])*

1.2.3 Fibrinolytic drugs

The first fibrinolytic substance was discovered in the first half of the 1930s[9], when it was observed that some strains of haemolytic streptococci were able to liquefy human fibrin clot. Almost 10 years later it was elucidated that the so-called 'streprococcal fibrinolysin' did not, in fact, directly cause the disintegration of the fibrin, but acted as a proteolytic enzyme cleaving an endogenous substrate, which then caused fibrinolysis.[10]

The substance was subsequently named streptokinase (SK), and was first used therapeutically to liquefy the congealed pleural effusions seen in empyema.[1] SK works by unselectively binding to plasminogen, forming a complex that can catalyse the change from plasminogen to plasmin. It therefore has an effect both on circulating plasminogen as well as plasminogen bound to fibrin, and thereby induces systemic plasminaemia. SK has subsequently been used in the treatment of both acute myocardial infarction[11] and lower extremity ischaemia.[12]

Although SK is an effective fibrinolytic, its antigenicity (secondary to its bacterial origin) can cause significant side-effects (hypotension and allergic reactions, to mention the most common) in patients, which limits its use. Moreover, the unselective nature of the plasminogen activation may increase the risk of haemorrhage.[3]

Urokinase (UK) was subsequently isolated from human urine in the 1950s. Unlike SK, UK is non-antigenic[13] but possesses similar fibrinolytic activity. Compared with SK, UK has an increased affinity for fibrin-bound plasminogen, thereby reducing systemic fibrinolysis.[14]
Because of its improved safety profile, UK became the preferred lytic agent until the 1980s, when recombinant t-PA (rt-PA) was brought onto the market[15].

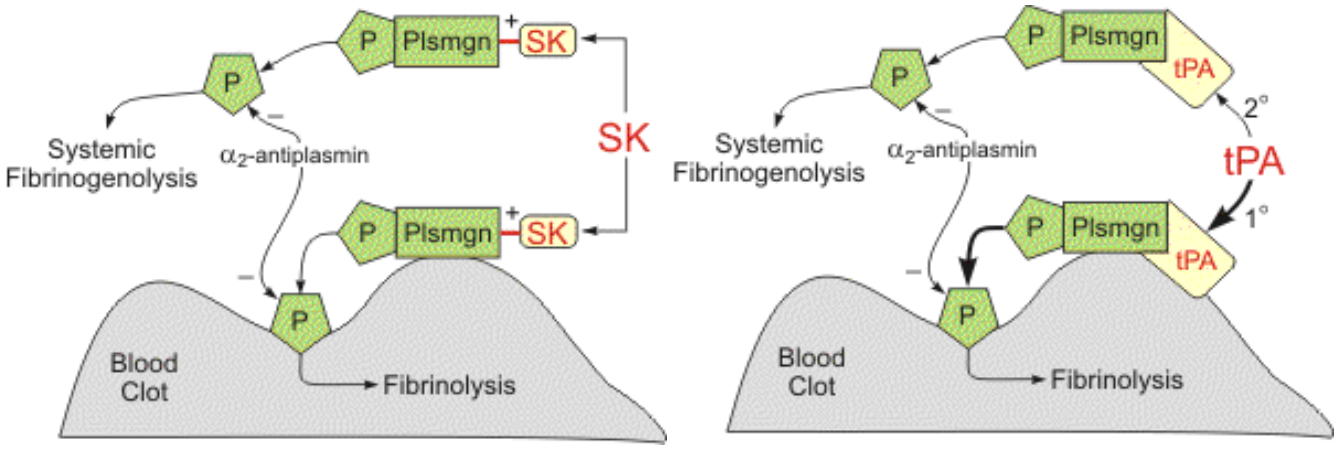

Figure 2: *Mechanism of action of SK and t-PA (used with permission from Dr R.E. Klabunde)*

First produced on a larger scale using DNA-technology at the start of the 1980s by Pennica and colleagues[15], rt-PA has since been in common use for the treatment of myocardial infarction, stroke, lower extremity ischaemia and deep venous thromboembolism.
Naturally occurring t-PA is a single-chain serine protease that is converted by plasmin to a two-chain form. Both the single and the two-chain forms have enzymatic activity and rt-PA is a combination of the two forms, although the single-chain forms dominates.[15] The half-life of rt-

PA in plasma is five minutes.[16] Compared with SK, rt-PA has been shown to reduce overall mortality in AMI, although at a slightly increased risk of intracranial haemorrhage.[17] It has been used extensively in several different clinical settings and is currently the only agent approved for use in acute ischaemic stroke.[16] *Figure 2* shows a graphical representation of the mechanism of action of SK and rt-PA.

Further advances have been made to identify thrombolytic agents that potentially carry a reduced risk of unwanted side-effects.[18] An ideal thrombolytic agent would be one that provides quick and efficient clot lysis at the site of the thrombus or embolus but does not induce systemic fibrinolysis, reducing the risk of bleeding at remote sites.[19]

Newer developments include tenecteplase (TNK-t-PA), which is a mutated version of t-PA with substitutions at three sites of the original amino acid sequence. These substitutions reduce metabolism in the liver and cause an increased resistance to inactivation by circulating PAI-1, thereby increasing plasma half-life as well as increasing fibrin specificity (in theory reducing non-specific plasmin activation).[20] Tenecteplase has mainly been used in the setting of AMI[20], but also in the treatment of acute lower limb ischaemia.[21]

Reteplase is another bioengineered variety of t-PA where some of the domains of the original structure have been deleted, which has resulted in reduced fibrin binding and a longer half-life (14-18 minutes compared with 4-5 minutes for rt-PA). Like tenecteplase, reteplase has mainly been used in AMI, where it has been studied in e.g. the GUSTO III[22] and the INJECT[22] trials. These trials failed to show a reduction in AMI-related mortality for reteplase, but the INJECT study showed a reduction in morbidity compared with those receiving rt-PA.

Another novel fibrinolytic is pro-urokinase. This is a precursor to UK that binds to fibrin. On binding to fibrin, the single-chain molecule of pro-UK is cleaved into the two-chain configuration of full molecular weight UK, which enhances its activity up to 1,000-fold.[23] Pro-UK shows an increased fibrin specificity compared with UK. It has been used in AMI[24] and for treating lower limb ischaemia in the PURPOSE trial.[25]

There has also been development of direct-acting plasmin activators, i.e. substances that do not require the activation of plasminogen.

Alfimeprase is a recombinant derivative of fibrolase, a metalloproteinase found in southern copperhead snake venom. This enzyme directly cleaves the Aα chain of fibrinogen without the need for activation of the endogenous fibrinolytic system.[26] This leads to a quicker onset of action of thrombolysis. Alfimeprase is inactivated by α2-macroglobulin, an endogenous inhibitor of metalloproteinases.[26] This inhibition is rapid and theoretically reduces the risk of remote-site bleeding. However, it makes catheter-based delivery of alfimeprase directly into the thrombus necessary, as systemic administration would lead to its immediate degradation.
Clinically, alfimeprase has been used most recently in a controlled trial by Han and colleagues comparing alfimeprase and placebo for CDT of acute lower limb ischaemia.[27] However, this

trial failed to show any benefit in terms of avoidance of subsequent open surgery compared with placebo.

Plasmin itself has also been investigated as a possible thrombolytic. In the setting of systemic thrombolysis, direct administration of plasmin would be unfeasible because of its rapid degradation by α2-antiplasmin in the circulation. However, like alfimeprase, intra-thrombus delivery (as used in CDT) would theoretically be possible, and the method is currently being evaluated in the PRIORITY trial for treating patients with peripheral arterial thrombosis.[28]

***Table 1*:** Common fibrinolytic agents in clinical use

	Origin	Indications	Half-life (min)
rt-PTA	Recombinant	Stroke, AMI, Peripheral arterial occlusion, DVT, pulmonary embolism	5
SK	Streptococcus	AMI, peripheral arterial occlusion, DVT, pulmonary embolism	20
UK*	Cell culture	AMI, pulmonary embolism, DVT, peripheral arterial occlusion	15
Reteplase	Recombinant	AMI, peripheral arterial occlusion	15
TNK-t-PA	Recombinant	AMI	15

*Not currently available

1.3 THROMBOLYSIS IN PRACTICE APPLICATIONS, OUTCOMES AND COMPLICATIONS

1.3.1 Acute limb ischaemia

Since the study by Dotter and colleagues in 1974[2], in which low-dose streptokinase was administered for the first time directly into the target vessel using a catheter-directed approach in patients with acute lower extremity ischaemia, CDT has become widely used in the treatment of this very large group of patients. The selective delivery of the thrombolytic agent into the thrombus itself or the immediate surrounding area decreases the degree of systemic fibrinolysis[29], and the method is readily combined with other endovascular techniques in order to e.g. correct any underlying culprit lesion, which provides a theoretical advantage over traditional open embolectomy or thrombectomy. However, due to its mechanism of action, the onset of lysis and thus time to reperfusion may be slower compared with open surgery, which limits its use to patients whose limbs are not immediately threatened.

During the 1990s, Ouriel and colleagues performed three randomised, controlled trials (Ouriel 1994[30], STILE[14] and TOPAS[31]) with a total of 951 patients comparing open surgery with thrombolysis using either rt-PA or UK. Subgroup analyses were subsequently performed using data from the STILE-cohort, resulting in a further two publications reporting on outcomes in native vessels[32] and bypass grafts.[33]

In the STILE trial, the risk of death and amputation was similar for CDT compared with open surgery, although there was an increase in all-cause morbidity in those patients undergoing thrombolysis, which caused the trial to be stopped prematurely. Moreover, in a subgroup analysis of the data from this study, it was noted that occlusion of native arteries was associated with a higher risk of amputation for CDT compared with open surgery, whereas bypass graft occlusion of less than 14 days' duration fared better after CDT than surgery.[14]
In the TOPAS trial, there was no difference in overall and amputation-free survival between the CDT and the open surgery groups (68% amputation-free survival at one year).[31]

In an updated Cochrane review, Berridge and colleagues[34] examined the cumulative results of available randomised trials comparing thrombolysis with open surgery for the initial management of acute limb ischaemia. In this review, the above trials (STILE and TOPAS) were included together with a publication by Nilsson and co-workers[35] in which the authors randomised 20 patients to either thrombolysis with rt-PA (n=11) or open surgery. In this study, there were no differences in death, amputation or stroke at 30 days, although the event rate was low with only one amputation and one death (both in the surgery group) and no events in the thrombolysis group.

In a pooled analysis of the randomised trials above, there was a significantly higher risk of bleeding (odds ratio 2.8; 95% CI 1.7-4.6), stroke (OR 6.41; 95% CI 1.57-26.22) and distal embolisation (OR 8.35; 95% CI 4.47-15.58) in the thrombolysis patients, although thrombolysis did reduce the level of surgery required at 30 days (OR 5.37; 95% CI 3.99-7.22). There were no significant differences in amputation-free survival or death at 30 days or one year. Based on the available evidence, the Cochrane review concluded that there is no evidence either to support or discourage the use of thrombolysis over open surgery for patients.

It is important to note that the included studies were very heterogenous in terms of duration of ischaemia, thrombolysis protocols used (duration and type of thrombolytic agent) and also differed with regards to reporting standards. Furthermore, given that the most recent of the included trials was performed almost 10 years ago, it is unclear whether the results are directly applicable today, as there have since been technical advances made within the endovascular field.

In a more recent study, Kuoppala and colleagues reported on 220 patients who had undergone thrombolysis for acute limb ischaemia. In this study, the amputation-free survival was in excess of 80% at one year with a frequency of bleeding complications of 33%, although only 6% of these patients required premature cessation of thrombolysis. In subsequent multivariate analyses of factors associated with amputation during follow-up, degree of lysis, severity of ischaemia (motor deficit and presence of ulcers) and ischaemic heart disease were found to be independent predictors of loss of limb.

Thrombolysis has also been shown to be beneficial in the particular case of patients presenting with occlusion of a popliteal artery aneurysm, where use of the technique prior to arterial reconstruction led to an improvement of the distal run-off from the occluded aneurysm and thereby leg-salvage.[36]

1.3.2 Thrombolysis for stroke

The first large investigation of the use of thrombolysis for the treatment of acute stroke was the National Institute of Neurological Disorders trial (NINDS), which was published in 1995.[37] This study was actually a joint report of two connected trials with a total of 624 included patients, and showed a significant improvement in disability (as measured by a reduction in the National Institutes of Health Stroke Stroke Scale (NIHSS)) for patients who were treated with intravenous (i.e. systemic) rt-PA within three hours after the onset of stroke symptoms. In the NINDS trial, the frequency of symptomatic intracerebral haemorrhage after thrombolysis was reported as 6.4%. There have since been further large trials comparing rt-PA with placebo for the treatment of stroke, and in a meta-analysis of 6,756 patients[38], rt-PA was shown to increase the chance of a reduction in disability compared with placebo for all time points up to 4.5 hours after the onset

of symptoms with a maximum benefit seen within three hours (OR 1.75; 95% CI 1.35-2.27) after onset of symptoms. A 'good' outcome was defined as an absence of significant disability at three or six months following the initial stroke, i.e. by a modified Rankin score of 0 to 1. There was a significantly increased risk of symptomatic intracranial haemorrhage following rt-PA compared with placebo with an O.R of 5.55 (95% CI 4.01-7.7) and of fatal intracranial haemorrhage (OR 7.14; 95% CI 3.14-12.58). However, there was no difference in mortality between the groups (hazard ratio 1.11; 95% CI 0.99-1.25). The compound conclusion drawn from this comprehensive analysis was that although rt-PA increases the risk of intracranial haemorrhage, this risk is offset by an increased likelihood of a good outcome after stroke if given within 4.5 hours after symptom onset, with benefits proportionally greater if treatment is given earlier.

Based on the available evidence, thrombolysis has become widely used in the acute management of stroke, which naturally has led to a significant increase in the number of patients receiving this treatment. A review of data published by the Swedish Stroke Registry (Riks-Stroke) shows that the number of patients receiving cerebral reperfusion therapy (i.e. thrombolysis or catheter-directed thrombectomy) has more than doubled since 2010 (5% in 2010 to over 12% in 2014).[39] In a study from 2009, Gladstone and colleagues[40] noted that the number of patients presenting with either a transient ischaemic attack (TIA) or stroke who had a concomitant significant carotid artery stenosis (50-99% lumen reduction), and were therefore possible candidates for carotid intervention, was in the region of 10% (1011 of 10 213 patients).

The number of patients receiving thrombolysis for stroke who then proceed to carotid surgery or stenting may therefore be expected to increase. However, prior thrombolytic therapy may bring an altered spectrum of complications to this patient group, in particular with regards to periprocedural stroke, intracranial haemorrhage and perioperative bleeding. There have been a few studies examining smaller cohorts of patients undergoing carotid endarterectomy (CEA) after thrombolysis for stroke, but none of these have conclusively demonstrated an increased risk of adverse events.[41-44] A recent systematic review of a total of 114 patients who had undergone CEA or stenting after stroke thrombolysis showed similar rates of stroke and death within 30 days compared with patients who had not undergone prior thrombolysis.[45]

1.3.3 Thrombolysis for dialysis access thrombosis

In 2011, there were more than two million patients undergoing haemodialysis treatment (HD) for end-stage renal failure (ESRF) worldwide.[46] For these patients, a functioning vascular access is a necessity. A vascular access may be an autologous fistula (AVF; i.e. a non-anatomical arteriovenous connection between a native artery and a native vein), an arteriovenous graft (AVG; i.e. an arteriovenous connection using a synthetic conduit) or a central dialysis catheter. AVFs and AVGs are generally preferred over dialysis catheters, as they have been associated with improved patient survival and reduced morbidity.[47]

Dialysis access thrombosis is unfortunately a very common complication affecting both AVFs and AVGs, resulting in significant patient morbidity and healthcare-associated costs.[48]

As with acute limb ischaemia, access thrombosis has traditionally been treated using open surgical thrombectomy for removal of the offending thrombus. However, this may lead to failure in treating any underlying culprit lesion not immediately obvious at the surgical site. Alternative endovascular strategies may therefore offer a treatment advantage, as they allow for a visualisation of access anatomy and the possibility to correct remote lesions during the same session.

Thrombolysis for dialysis access thrombosis was first described in 1985[49], when Zeit and colleagues instilled SK solution through multiple needle puncture sites of thrombosed AVGs. In this early cohort, 73% of patients had successful recanalisation of their access, although 30% required subsequent corrective surgery. Thrombolysis has subsequently been used with increasing frequency, often in the form of the 'lyse and wait' technique introduced in 1997[50] in which the thrombolytic agent in a mix with heparin was instilled into the AVG during occlusion of the arterial and venous ends. However, there remains a relative paucity of evidence surrounding endovascular treatment of the thrombosed native fistula.

In a report by Rajan and colleagues[51], a 73% immediate success rate and an assisted primary patency of 43% at 43% at three months were achieved after bolus injection of UK or rt-PA. In a more recent series, it was noted that technical success following endovascular treatment was lower for AVFs than AVGs, with reported angiographic success-rates of 80.3% compared with 93.7% for the grafts.[52]

A meta-analysis of studies comparing outcomes after endovascular procedeures with open surgery for dialysis access thrombosis did not reveal any significant differences in technical success (OR 1.4; 95% CI 0.91-2.14), 30-day primary patency (OR 1.14; 95% CI 0.79-1.68), need for central dialysis catheter (OR 0.77; 95% CI 0.44-1.34) or morbidity (OR 1.12; 95% CI 0.67-1.86). On the other hand, there was a trend towards an increase in 1-year patency for those having undergone open surgery (OR 2.08; 95% CI 0.97-4.45). However, the studies included in the meta-analysis employed a variety of techniques, such as pharmacomechanical thrombolysis (the use of a catheter device to fragment the thrombus; see below for further discussion), under the endovascular umbrella. The resulting heterogeneity limits the applicability of the findings.

Factors that may affect the risk of reocclusion after surgery or endovascular treatment of access thrombosis were studied by Crikis and colleagues.[53] These authors did not detect any difference in the risk of reocclusion after initial endovascular treatment for access thrombosis between AVFs and AVGs, although the risk of a second reocclusion was higher for AVGs compared with AVFs (rate ratio 0.3; 95% CI 0.11-0.8). In this study, a history of previous deep venous thrombosis (DVT) was also found to increase the risk of a second reocclusion (rate ratio 4.14; 95% CI 1.3-13.09), whereas on-going anticoagulant treatment with either warfarin or heparin significantly lowered the risk (rate ratio 0.14; 95% CI 0.04-0.71).

1.3.4 Other frequently used applications of thrombolysis

Deep venous thrombosis:
Both systemic and catheter-directed thrombolysis have been used in the treatment of deep vein thrombosis (DVT). The aim of treatment is to reduce the risk of subsequent pulmonary embolism, induce venous recanalisation and reduce the risk of development of the post-thrombotic syndrome, a state of chronic deep venous insufficiency that can cause leg swelling, oedema, venous eczema and ultimately venous ulceration. Compared with standard treatment with low-molecular weight heparin alone, thrombolysis more frequently results in venous patency (risk ratio 4.9; 95% CI 1.66-14.53) and reduced risk of the post-thrombotic syndrome (relative risk 0.64; 95% CI 0.52-0.79), but also an increased risk of peri-procedural bleeding (relative risk 2.23; 95% CI 1.51-3.52).[54] Based on the available evidence, current guidelines for the treatment of DVT recommend CDT if the following criteria are met: symptoms of <14 days, good functional status, life-expectancy of more than one year and low risk of bleeding.[55]

Pulmonary embolism:
Systemic thrombolysis has been used in the treatment of pulmonary embolism (PE). In theory, thrombolysis offers enhanced clot lysis and a reduced time to pulmonary vascular patency. However, there is still uncertainty as to which patients benefit the most from such treatment. In a recent Cochrane review, currently available evidence (comprising 2,167 patients in the selected studies) was examined comparing thrombolysis with heparin alone.[56] Compared with heparin, thrombolysis showed a reduction in all-cause mortality (odds ratio 0.57; 95% CI 0.37-0.87) and PE recurrence (OR 0.51; 95% CI 0.29-0.89), but a higher risk of bleeding (OR 2.9; 95% CI 1.95-4.31 for major bleeding and OR 3.03; 95% CI 1-6-5.73 for minor bleeding).[56]

There is currently no clear evidence to support the use of catheter-directed intervention as opposed to systemic thrombolysis, and there is no reported clinical trial comparing these strategies head-to-head.[57]

Upper limb deep venous thrombosis:
CDT has also been used in the setting of upper limb deep vein thrombosis. This is commonly seen in malignancy (more than 40% of patients with upper limb DVT are found to have some form of malignancy during subsequent investigations), in patients with indwelling central venous catheters and in patients with the thoracic outlet syndrome (TOS; a narrowing of the thoracic aperture causing extrinsic compression of the subclavian vein and/or artery).[58] There is currently relatively limited evidence for the role of CDT in this patient group and no randomised studies comparing this treatment with heparin alone.[59] In the case of TOS, patients are often treated with initial CDT to restore venous patency, after which surgical decompression of the thoracic outlet is undertaken.[58]

Central venous catheter occlusion:

In addition to upper limb DVT, central venous catheter dysfunction may also be caused by the formation of a fibrin sheath that occludes the catheter tip. Semba and colleagues reported on two phase III trials, comprising 1,064 patients, of rt-PA for use in central venous catheter (CVC) thrombosis.[60] In these studies, 2mg of rt-PA was instilled locally into the occluded CVC and left for 120 minutes. Success was achieved in 75% of patients after one dose of rt-PA, which rose to 85% after two doses. There were no serious adverse outcomes such as intracranial haemorrhage or significant bleeding.

1.3.5 Pharmacomechanical thrombolysis

In addition to purely pharmacological thrombolysis via either the systemic or intra-arterial routes, several endovascular devices have been developed with the aim of providing quicker thrombus fragmentation and thereby quicker restoration of vessel patency. The use of such adjuncts may be referred to as pharmacomechanical thrombolysis (PMT).

Please see *Table 2* for a brief summary of the most common available devices.

***Table 2*:** Common pharmacomechanical thrombectomy devices

Device	Mechanism of action	Applications
Arrow Trerotola	Rotational – metal basket at tip of catheter for fragmentation of thrombus	Dialysis access thrombosis, pulmonary embolism
Amplatz thrombectomy device	Rotational – impeller at tip of catheter rotates rapidly pulling thrombus towards tip, causing fragmentation	Dialysis access thrombosis
Rotarex®	Rotational – spiral at tip of catheter 'drills' into thrombus, central vacuum at tip draws thrombus into catheter where it is removed	Peripheral arterial thrombosis, DVT, dialysis access thrombosis
Trellis®	Oscillating wire between two balloons for thrombus fragmentation plus infusion of thrombolytic in treated segment	DVT, peripheral arterial thrombosis
AngioJet®	Rheolytic – high-speed saline jets from tip of catheter create pressure gradient leading to fragmentation and evacuation of thrombus	DVT, peripheral arterial thrombosis, PE, dialysis access thrombosis
EKOS®	Emission of ultrasonic waves thins fibrin component and enhances transportation of fibrinolytics into the target thrombus	DVT

All the above devices carry a theoretical risk of vascular endothelial injury secondary to the trauma induced by the device, as well as a risk of haemolysis.[61] The AngioJet® device has also been associated with the development of bradyarrhythmias, especially if the device is used close to the heart.[62] The exact mechanism of this has not been elucidated, but is thought to involve the Bezold-Jarisch reflex[63], a vagally mediated response to certain chemical stimuli within the heart.[64]

There have so far been few randomised trials comparing PMT with CDT, especially in the setting of lower limb ischaemia.

In the case of dialysis access thrombosis, Uflacker and colleagues compared the outcomes of PMT using the Amplatz device with surgical thrombectomy but did not detect any significant differences in immediate success (thrombus clearance and ability to dialyse using the access) or patency at 30 and 90 days post-procedure between the groups.[65] In another study, the AngioJet® device was compared with open thrombectomy for thrombosis of prosthetic dialysis grafts. There was no difference in immediate success between open surgery or PMT, but there was a trend toward better patency in the open surgery group at both one and three months (41% versus 31% at one month and 26% versus 15% at three months).

In the setting of acute limb ischaemia, Byrne and co-workers conducted a retrospective review of 154 patients having either undergone CDT or PMT using the AngioJet® device for the treatment of acute limb ischaemia.[66] In this study, there were no significant differences in overall primary patency, limb loss or complications between CDT and PMT, although PMT was associated with increased technical success rates compared with CDT (90.1% versus 78.3%; P=0.047).

1.4 TECHNICAL AND PRACTICAL ASPECTS OF THROMBOLYSIS

1.4.1 Patient selection

Careful patient selection is essential in order to minimise the risks of complications during systemic and catheter-directed thrombolysis. Moreover, the timing of treatment is important to ensure maximum benefit of treatment. In the setting of acute stroke, the American Heart Association and American Stroke Association (AHA/ASA) have produced joint guidelines to support clinical decision-making surrounding thrombolytic therapy.[67] The indications and contraindications for intravenous thrombolysis for stroke are summarised in *Table 3* below.

***Table 3*:** Indications and contraindications for thrombolysis in acute ischaemic stroke.[67]

Indications	Contraindications
Ischaemic stroke causing measurable neurological deficit	Head trauma < 3 months prior
Neurological signs not minor/isolated and not clearing spontaneously	Myocardial infarction < 3 months prior
No symptoms suggestive of subarachnoid haemorrhage	Gastrointestinal/genitourinary bleeding within 3 weeks
Onset of symptoms less than 3 hours prior	Major surgery < 14 days prior
	Non-compressible arterial puncture <7 days
	INR >1.7 and/or normal activated prothrombin time
	Recent trauma with active bleeding
	Platelet count $<100x10^9$/L
	Recent seizure with postictal impairment
	Multilobar infarction on CT
	Blood glucose <2.8mmol/L or >22 mmol/L
	Pregnancy

In the setting of CDT for peripheral arterial occlusions, *Table 4* outlines contraindications for treatment.

***Table 4*:** Absolute and relative contraindications for catheter-directed thrombolysis

Absolute	Relative
Active/ongoing bleeding	Cardiopulmonary resuscitation within 10 days
Gastrointestinal bleeding <10 days	Major surgery/trauma <10 days
Stroke/TIA <2 months	Systolic blood pressure >180mmHg or diastolic >110mmHg
Neurosurgery or intracranial trauma < 3 months	Intracranial tumour or arteriovenous malformation
	Severe limb ischaemia with motor and sensory deficit
	Recent eye surgery
	Diabetic haemorrhagic retinopathy
	Hepatic failure
	Bacterial endocarditis
	Pregnancy

In addition to the above, in order to be eligible for CDT patients must be able to undergo endovascular treatment and to follow instructions by medical and nursing staff such that safe siting of an indwelling intra-arterial catheter for the duration of treatment can be achieved.

1.4.2 Administration of the thrombolytic agent

For intra-arterial CDT, thrombolysis is performed via an indwelling catheter with multiple side-holes through which the thrombolytic agent is infused into the target vessel. In the case of lower limb ischaemia, vascular access is established through either an ante- or retrograde approach to the common femoral artery, often using ultrasound-guided micro-puncture. A vascular sheath is placed, through which the thrombolysis catheter is advanced over a guide-wire under fluoroscopic guidance. The aim is to place the tip of the catheter into the thrombus itself, or if it is not possible to pass the occlusion with the guide-wire, the catheter is placed as close to the thrombus as possible. The infusion of thrombolytic agent is then started, with or without a preceding bolus. In the case of rt-PA, a solution of drug diluted to 0.1mg/ml is often used and infused at rates of 0.5-1mg/h (i.e. 5-10ml/h). Control angiograms are then undertaken at varying frequencies depending on local guidelines and the clinical setting. Clot lysis is commonly seen after six to 24 hours. During the infusion, low-molecular weight heparin (LMWH) is often given at regular intervals to prevent sheath thrombosis. Alternatively, a continuous infusion of

unfractionated heparin (UFH) adjusted to activated partial thromboplastin time (APTT) may be used.

A similar protocol is used for dialysis access thrombolysis, although here two catheters may be placed in crossing directions in order to deliver the thrombolytic agent to both the arterial and venous limbs of the AVF/AVG.

Patients undergoing CDT are commonly cared for in an intensive or intermediate care setting for continuous monitoring of haemodynamic parameters, development of complications (e.g. bleeding) and limb status (in the case of acute limb ischaemia). In some vascular centres, patients undergo observation on a general surgical/vascular ward during CDT. It is unclear whether this confers a greater risk of complications and adverse events compared with a high-dependency setting.

In the treatment of acute ischaemic stroke, the currently used protocol involves the intravenous administration of rt-PA in a dose of 0.9mg/kg, 10% of which is administered as a bolus over one to two minutes followed by the remaining 90% as an infusion over 60 minutes.[68] Patients should preferably be treated at an institution with a stroke centre or if not, an rt-PA infusion may be started at the receiving hospital while awaiting transfer to a stroke centre.

1.4.3 Monitoring of thrombolytic therapy

Currently, there is no specific laboratory test to assess the efficacy of thrombolysis[69], although there are tests that will indicate the function of the various components of the coagulation system, as well as assays for assessing the degree of systemic fibrinolysis. During intra-arterial CDT, measurement of fibrinogen levels are undertaken in most centres to assess fibrinolysis, and the thrombolytic infusion may be stopped if the fibrinogen level falls below 1g/L or if there is an obvious trend of falling levels. The Clauss method is most commonly used in clinical settings.[70]

In addition, coagulation is monitored by measuring the prothrombin time (PT), which is an indicator of the function of the tissue factor pathway (factors V, VII, X and fibrinogen), and the activated partial thromboplastin time (APTT), which assesses both the contact activation (factors XII, XI and prekallikrein) and common pathways of the coagulation cascade.[71]

More recently, there have been investigations into the role of viscoelastic methods, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), in the setting of thrombolysis and also trauma. These methods provide a measurement of clot formation, strength and fibrinolysis.[72] However, they are not yet used on a larger scale for the routine monitoring of patients undergoing thrombolysis.

2 AIMS OF THE THESIS

The overall aim of this thesis was to examine the role, outcomes and safety of thrombolysis in the setting of vascular surgery. More specifically, the aims were:

I. To assess the clinical outcomes after thrombolysis in patients with lower limb ischaemia secondary to the occlusion of an infrainguinal bypass graft

II. To evaluate the safety of early carotid endarterectomy and carotid artery stenting in patients who had undergone systemic thrombolysis for stroke

III. To compare the clinical outcomes of thrombolysis with those of open surgical thrombectomy in patients with thrombosis of native and prosthetic dialysis accesses

IV. To investigate the role of the level of care in patient safety during intra-arterial thrombolysis

3 PATIENTS AND METHODS

3.1 STUDY DESIGN AND STUDY POPULATIONS

Patients were identified through local databases of radiological and surgical procedures at the participating hospitals (Studies I, III, IV) based on codes for the interventional procedures performed during the study time periods.

For Study II, the Swedish Vascular registry (Swedvasc) was used in conjunction with the Swedish Stroke registry (Riks-Stroke) for identification of the patients during the study time period. Please see *Table 5* for an overview of the study designs and patient populations.

***Table 5*:** Study designs and patient populations in the constituent studies

	Patients and study period	Design and methods	Centres
Study I	All patients (n=123) undergoing CDT for infrainguinal bypass graft occlusion 2000-2008	Retrospective cohort study of treatment outcomes and risk factors for technical failure, amputation and mortality	Karolinska University Hospital and Skåne University Hospital
Study II	Patients undergoing carotid endarterectomy or stenting 2008-2012 with (n=79) or without (n=3919) preceding thrombolysis for stroke	Retrospective analysis of prospective data collected from Swedvasc, Riks-Stroke and individual patient records. The influence of thrombolysis on outcomes was assessed	Nationwide (Sweden)
Study III	All patients (n=131) undergoing CDT or open thrombectomy for primary dialysis access thrombosis 2005-2013	Retrospective cohort study with regard to outcomes after open or endovascular treatment	Karolinska University Hospital and South General Hospital
Study IV	All patients (n=252) undergoing CDT for limb ischaemia or dialysis access thrombosis between 2005-2013	Retrospective cohort study of safety-outcomes of two different care regimes during CDT and risk factors for patient transfer to a higher level of care	Karolinska University Hospital and South General Hospital

3.2 ETHICAL CONSIDERATIONS

3.2.1 Study I

Study I was a quality audit of the outcomes of thrombolysis for the treatment of patients with occlusion of an infrainguinal bypass graft. Patients had already been treated using standard protocols and there was no effect on patient care and follow-up. Patients had been treated either at Karolinska University Hospital in Stockholm, Sweden or Skåne University Hospital in Malmö, Sweden. The Malmö cohort was a subgroup of patients already used in a larger prospective analysis of infrainguinal thrombolysis for which ethical approval had already been granted. The regional ethics board in Lund, Sweden had no reservations concerning study design and data collection. This, together with the permission from the local Head of Department to conduct a quality assurance audit, was considered adequate with regards to ethical analysis.

3.2.2 Studies II-IV

These studies were granted ethical permission from the regional ethics committee in Stockholm. As above, patients had already been treated using standard protocols and none of the studies influenced the follow-up of any of the patients. All data was collected from medical records, digital radiological databases (PACS-systems) and national quality registries (Study II). For Study II, written informed consent for accessing individual medical records was sought from patients or relatives (if patients were unable to give consent themselves). No such consent was deemed necessary by the ethics committee for Studies III and IV.

3.3 PATIENTS AND METHODS STUDY I

The aim of this study was to assess the outcomes of catheter-directed thrombolysis in patients with thrombosis of an infrainguinal bypass graft and to examine any risk factors for adverse outcomes (technical failure, amputation and death).

Study population

The cohort consisted of all patients (n=123) who had been treated with CDT for infrainguinal bypass graft occlusion at Skåne University Hospital in Malmö and at Karolinska University Hospital in Stockholm. These two hospitals are tertiary referral centres for vascular and endovascular surgery, and have a combined catchment area of approximately 1.8 million people. The respective hospital database of radiological procedures was used to identify the patients. The study period was January 1, 2000 (Karolinska) and January 1, 2001 (Malmö) to December 31, 2008.

Study intervention

All patients underwent CDT according to the protocol of the treating hospital. Briefly, patients were screened for the presence of any contra-indication, after which blood tests for clotting function were taken. Any previously performed imaging (computer tomography, duplex ultrasound, magnetic resonance imaging) was scrutinised before commencement of thrombolysis. Arterial access was established in the ipsi- or contralateral common femoral artery. A guide-wire was then used to pass the thrombus, whereafter a thrombolysis catheter with multiple side-holes was placed inside the thrombus. An infusion of rt-PA (Actilyse, Boehringer-Ingelheim) was then commenced at a rate of 1-2mg/h. Patients received either LMWH (Karolinska) or continuous UFH (Malmö) during thrombolysis to prevent sheath thrombosis. Control angiograms were performed at regular intervals depending on the clinical and radiological picture. Fibrinogen, PT and APTT were monitored at regular intervals according to local protocol.

Data collection and outcome measures

A retrospective review of the medical records of the included patients was conducted, which also included scrutiny of the radiological data from the endovascular procedures performed as part of the treatment. Mortality data was accessed via the patient records, which were linked to the Swedish Population Registry. *Table 6* summarises the variables and their definitions.

***Table 6*:** Variables and their definitions

Variable	Definition
Hypertension	Systolic blood pressure >140mmHg or diastolic BP or >90mmHg or documented prescription of antihypertensive medication
Cerebrovascular disease	Previous documented history of either a manifest stroke or transient ischaemic attack (TIA)
Ischaemic heart disease	Previous history of myocardial infarction, angina pectoris, coronary artery bypass grafting or percutaneous coronary intervention
DM	Documented DM treated either by diet, oral hypoglycaemic agents or insulin
Atrial fibrillation	History of atrial fibrillation
Acute critical ischaemia of the lower limb	Sudden impairment in limb perfusion causing a threat to tissue viability
Technical failure	Insufficient degree of lysis – either no lysis or lysis without run-off on completion angiogram
Additional interventions	Endovascular, open or combined (hybrid) procedures undertaken during the same inpatient episode
Major amputation	Amputation above the level of the tarsometatarsal joint
Major haemorrhage	Bleeding requiring surgical intervention or blood transfusion or cessation of thrombolysis

Statistical analysis

Statistical analysis was undertaken using IBM SPSS version 18. Continuous variables were expressed as mean ± standard deviation. Univariate analyses were undertaken using Pearson's X^2, Fisher's exact test, Cramer's V and Kendall's Tau. Logistic regression was undertaken to identify variables associated with technical failure (a binary variable), and Cox regression was used to examine predictors of amputation and death. Survival analysis (amputation-free survival and patient survival) was performed using the Kaplan-Meier estimator.

3.4 PATIENTS AND METHODS STUDY II

The aim of this study was to asses whether prior systemic thrombolysis for stroke affects the outcomes in patients subsequently undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS) for symptomatic carotid artery stenosis. The study consisted of patients from all vascular centres in Sweden where CEA and/or CAS are performed (n=22).

Study population

The study included all patients who had undergone CEA (n=71) or CAS (n=6) during the study period from May 1, 2008 to December 11, 2012 (n=3,998). Please see *Figure 3* for a flow-chart of the study population.

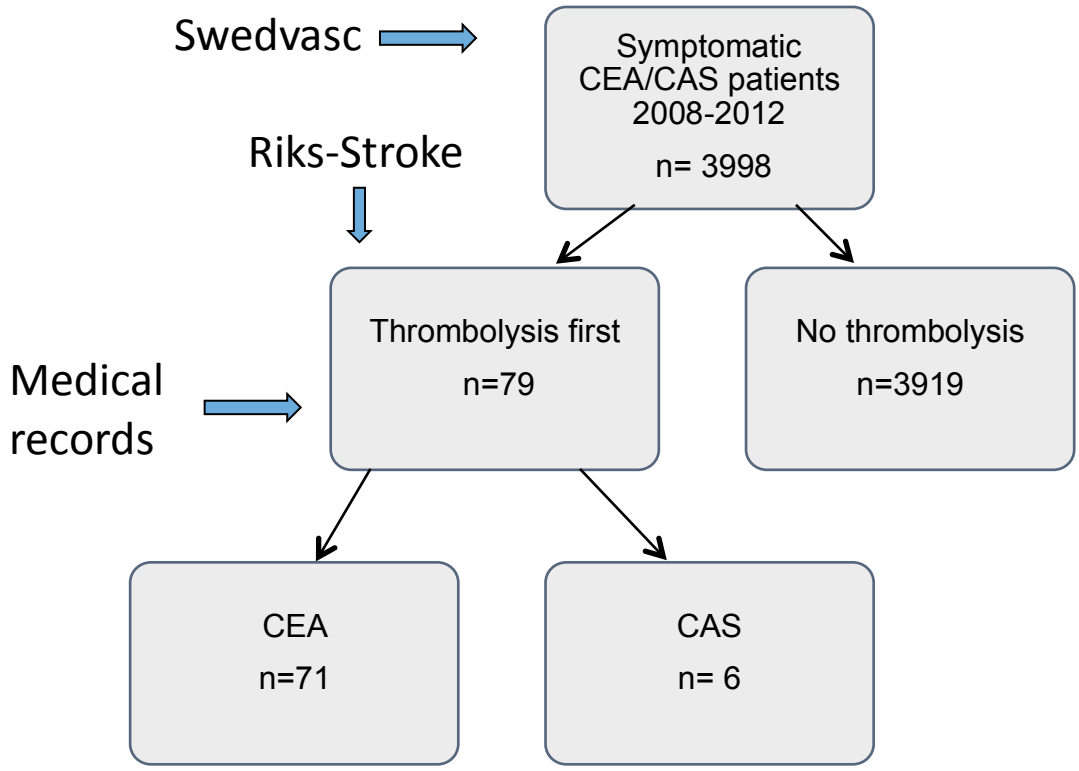

Figure 3: *Flow chart of patients included in study IV*

Study interventions

Carotid endarterectomy

Open surgery was performed under general or local anaesthesia depending on local protocol. Shunt use was left to the discretion of the operating surgeon. In some centres, eversion endarterectomy was performed, although the majority of centres performed a standard patch procedure.

Carotid artery stenting

CAS was undertaken under local anaesthesia. All centres used cerebral embolic protection (filter or flow-reversal).

Data collection and outcome measures

Data from the Swedish Vascular registry and the Swedish Stroke registry was collected prospectively and analysed retrospectively in the study. Medical records were then double-checked to ensure completeness of data and to collect information on variables that were not available in any of the registries (type of anaesthesia, use of intraoperative anticoagulation). Please see *Table 7* for a summary of which data was collected from which source.

It should be noted that 19 patients withheld their consent for scrutiny of their medical records, which resulted in incompleteness of data concerning comorbidities.

***Table 7*:** Summary of data collection Study II

	Swedvasc	Riks-Stroke	Medical records
Age, sex	X		
Comorbidities	X	X	X
Medications		X	X
Index symptoms	X		X
Initial cerebral imaging		X	X
Neurological disability (modified Rankin score and NIHSS)		X	X
Degree of carotid stenosis	X		X
Type of carotid procedure	X		
Intraoperative details (type of anaesthesia, use of shunt, intraoperative anticoagulation)	X		X
Complications after CEA/CAS	X		X
30-day follow-up	X		X

Statistical analysis

All data was analysed using IBM SPSS version 21 with the addition of the online interface at http://www.quantpsy.org/fisher/fisher.htm for the calculation of Fisher's exact test. Descriptive statistics were calculated as appropriate and P-values <0.05 were considered statistically significant.

3.5 PATIENTS AND METHODS STUDY III

The purpose of this study was to compare the outcome of an endovascular approach with pharmacological thrombolysis with open surgery for the treatment of a first episode of dialysis access thrombosis. A secondary aim was to identify any factors associated with the risk of re-thrombosis following the initial procedure.

Study population

The study included all patients (n=131) presenting to Karolinska University Hospital and South General Hospital for a first episode (for the access in question) of dialysis access thrombosis between December 1, 2005, and December 31, 2013. *Figure 4* shows the distribution of the study interventions.

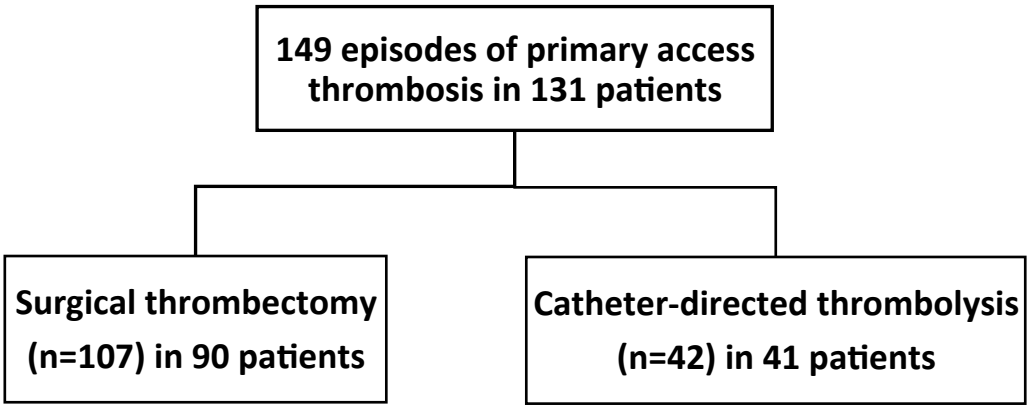

***Figure 4**: Distribution of the study interventions*

Study interventions

Patients underwent either pharmacological thrombolysis with indwelling catheter(s) or open surgery with Fogarty balloon thrombectomy. Patients undergoing pharmacomechanical thrombolysis without continuous infusion of rt-PA were excluded from the study. There was no formal treatment algorithm for the choice of endovascular or open treatment, and the decision regarding treatment type was left to the physician in charge.

Data collection and outcome measures

Data was collected retrospectively from patient medical records concerning comorbidities, aetiology of renal disease, concomitant antithrombotic medication and adjunctive procedures (any open or endovascular procedure undertaken as a complement to the index procedure during the same inpatient episode).

Patients were divided into four groups based on treatment (thrombolysis versus surgery), access anatomy and type (AVF versus AVG): (1) AVF thrombolysis, (2) AVF thrombectomy, (3) AVG thrombolysis and (4) AVG thrombectomy.

Patency was calculated as the time from either thrombolysis or thrombectomy and the next clinically verified access rethrombosis (if any). This was therefore the *post-intervention assisted primary patency*.[73]

Technical success was defined as at least one successful dialysis session (using the access in question) after the procedure.

Statistical analysis

Baseline demographic data was analysed using IBM SPSS version 21. Stata release 13 was used for all other analyses.

Patency time was calculated using the Kaplan-Meier method, and Cox regression was used to calculate crude and adjusted hazard ratios. Poisson regression was used to model the risk of rethrombosis over time for each of the four treatment groups.

3.6 PATIENTS AND METHODS STUDY IV

The aim of this study was to investigate whether the level of care influences the safety of catheter-directed intra-arterial thrombolysis. Traditionally, patients undergoing CDT have been cared for on a high-dependency ward with continuous monitoring of haemodynamic parameters for the early detection of complications such as bleeding. However, it is unknown whether care on a general ward offering a lower level of care is associated with an increase in adverse safety outcomes.

Study population

All patients (n=252) undergoing CDT for limb ischaemia or dialysis access thrombosis at Karolinska University Hospital (Centre 1) and South General Hospital (Centre 2) between January 1, 2012 and December 31, 2014 were included.

Study intervention

CDT was performed as described in Study I and III, and there was no difference in technical protocols between the hospitals. Patients at Centre 1 were cared for on a general vascular ward with standard nursing care and without invasive haemodynamic monitoring, whereas patients at Centre 2 were kept on the postoperative recovery unit where haemodynamic parameters (arterial blood pressure, ECG and pulse-oximetry) were continuously monitored and there was a decreased ratio of patients to nursing staff.

Data collection and outcome measures

In addition to baseline demographic variables, data was also collected regarding antithrombotic medication, bleeding and non bleeding-related complications, site of thrombolysis catheter (arm, groin, dialysis access), clinical success (angiographic and clinical evidence of improvement in vascular patency) and any conversion to open surgery or amputation during the same inpatient episode. Please see *Table 8* for a list of the complication-related variables and classification of bleeding used.

Statistics

All analyses were conducted using IBM SPSS version 23. Continuous variables were expressed as median and range unless otherwise specified. Univariate analyses of binary and nominal variables were conducted using cross-tabulations (values reported to Pearson's X^2 and Fisher's exact test). Variables associated with bleeding, non-bleeding complications and transfer to a higher level of care were entered into a logistic regression model with forced entry of the variables. Significant associations were expressed as odds ratios with 95% confidence intervals. Statistical significance was considered for P-values of less than .05.

***Table 8*:** Variables relating to outcomes Study IV

Variable		Definition
Acute myocardial infarction		Clinical signs consistent with the diagnosis and elevation of serum cardiac enzymes
Ischaemic stroke		Clinical signs consistent with the diagnosis and absence of intracerebral bleed on computed tomography
Haemorrhagic stroke		Clinical signs consistent with the diagnosis and radiological evidence of intracranial bleeding
Intractable pain		Pain not responding to treatment with standard doses of opiate and non-opiate analgesics, or requiring larger than expected analgesic doses
Confusion		Confusion or delirium severe enough to necessitate cessation of CDT or moving the patient to a higher level of care
Bleeding*	**Grade 0**	No evidence of bleeding
	Grade 1	Minor bleeding not requiring intervention
	Grade 2	Moderate bleeding requiring some form of intervention, e.g. compression, cessation of thrombolysis
	Grade 3a	Any transfusion with overt bleeding or overt bleeding with a drop in haemoglobin ≥3 to <5g/dL
	Grade 3b	Overt bleeding and haemoglobin drop <5g/dL or cardiac tamponade or bleeding requiring surgical intervention for control or bleeding requiring intravenous vasoactive drugs
	Grade5[§]	Fatal bleeding

*Bleeding was defined according to Mehran 2011.[74]

[§] Grade 4 (bleeding associated with coronary artery bypass grafting) was not applicable to this study.

4 RESULTS AND DISCUSSION

4.1 RESULTS AND DISCUSSION STUDY I

Study I examined the outcomes of catheter-directed thrombolysis for the treatment of native and prosthetic bypass graft occlusion.

Patient characteristics and clinical findings preceding thrombolysis
During the study period, there were in total 659 inpatient episodes for intra-arterial thrombolysis at the participating centres of which 123 were due to infra-inguinal bypass graft occlusion. A summary of patient characteristics can be found in the left hand column of *Table 9* below.

***Table 9*:** Patient characteristics and factors associated with adverse outcome and technical failure Study I

	Patients (%)	Technical failure (%)	Major amputation (%)	Mortality (%)	Major amputation or mortality (%)
All	123	18 (15)	34/122 (28)	57 (46)	65 (53)
Women	47 (38)	7 (15)	16/46 (35)	25 (53)	29 (62)
Age ≥ 80 years	26 (21)	4/26 (15)	8/25 (32)	19/26 (73)(p=0.002)	19/26 (73)(p=0.02)
Smoking	86/107 (80)	14 (16)	25 (29)	43 (50)(p=0.077)	48 (56)
Hypertension	88/122 (72)	14 (16)	27/87 (31)	48 (55)(p=0.005)	53 (60)(p=0.013)
Diabetes Mellitus	33 (27)	7 (21)	11 (33)	17 (52)	19 (58)
Ischemic heart disease	53/122 (43)	3 (6)(p=0.013)	14/52 (27)	28 (53)	30 (57)
Cerebrovascular disease	21/122 (17)	1 (5)	5/20 (25)	13/21 (62)	14/21 (67)
Atrial fibrillation	27/122 (22)	3 (11)	6/26 (23)	16/27 (59)	16/27 (59)
Medication					
Platelet aggregation inhibitor	87/119 (73)	14 (16)	23/86 (27)	39 (45)	46 (53)
Warfarin	26/119 (22)	3 (12)	9 (35)	11 (42)	12 (46)
Disease specifics					
Acute lower limb ischemia	88/119 (74)	12 (14)	26/87 (30)	47 (53)(p=0.008)	51 (58)(p=0.065)
Synthetic graft occlusion	82/122 (67)	9 (11)(p=0.092)	27 (33)(p=0.043)	39 (48)	46 (56)
Supra-inguinal proximal anastomosis	26/121 (21)	2 (8)	8 (31)	9 (35)	12 (46)
Graft stenosis, any	49/121 (4)	7 (14)	14 (29)	21 (43)	25 (51)
Adjunctive intervention	87/121 (72)	14 (16)	20/86 (23)(p=0.098)	40 (46)	45 (52)
Outcome					
Major haemorrhage	16/121 (13)	3 (19)	6 (38)	11 (69)(p=0.053)	12 (75)(p=0.057)
Technical failure	18/123 (15)	-	8 (44)(p=0.089)	10 (56)	11 (61)
Major amputation	34/122 (28)	-	-	27 (79)(p<0.001)	-

Nineteen patients (15.4%) underwent thrombolysis of their bypass graft more than once. Seventy-four per cent (89/120) of patients presented with acute critical limb ischaemia, 24% (29/120) had new-onset claudication. Only two patients were asymptomatic.

Bypass graft characteristics

Please see *Table 10* for a summary of the frequencies of different types of bypass grafts in the cohort. The median time between bypass graft placement and subsequent occlusion was 39.5 months (range 0.5-507 months). Sixty-seven per cent of grafts were synthetic (polytetrafluororethylene, Dacron or composite).

***Table 10*:** Graft anatomy and material*

Bypass graft anatomy	Patients (%)	Vein: synthetic
Aortobifemoral bypass	25(21)	0:25
Femoro-femoral cross-over	9 (7)	0:9
Femoropopliteal bypass above-knee	25 (21)	4:21
Femoropopliteal bypass below-knee	27 (22)	13:14
Femorodistal bypass	29 (24)	23:6
Two bypass grafts	6 (4)	0:6

*In two cases, it was not possible to ascertain graft anatomy.

Angiographic findings and adjunctive interventions

The median duration of thrombolysis was 19 hours (range one to 51 hours). Graft-related lesions such as graft stenosis or kinking were the most common finding at angiography (43%). The next most common finding was stenoses of the native recipient artery (27%). However, almost a quarter (23%) of patients had no discernible culprit lesion. Twenty-five (21%) patients had more than one angiographic lesion.Adjunctive interventions were undertaken in 86 patients (70%) of cases and of these, 47 underwent an endovascular procedure, 26 underwent open surgery and 13 underwent a hybrid (i.e. simultaneous open and endovascular) procedure.

Complications

Major haemorrhage occurred in 16 patients (13.2%), but this was not associated with the total administered dose of rt-PA, patient age or graft material (P=0.21, 0.52 and 0.19 respectively). There were two haemorrhagic strokes (1.6%) and three fatal myocardial infarctions (2.4%).

Factors associated with major adverse outcome and technical failure

Technical failure of thrombolysis occurred in 18 patients (15%). Older grafts had a higher likelihood of technical success, with a median graft age of 45 months (range 0.5 to 507 months) for those with successful thrombolysis compared with 10 months (range one to 120 months) for those with technical failure; P=0.014). Patients with ischaemic heart disease exhibited a lesser rate of technical failure (P=0.013). In a binary logistic regression model with heart disease, graft age and material as covariates, heart disease remained as an independent factor associated with technical success (O.R 4, 95% CI 1.1-15.1; P=0.04). Patients with heart disease were not treated more often with any antithrombotic medication compared with the remaining cohort (P=0.51).

The 30-day amputation rate was 11.4% (14/123), and at one year this had risen to 25.4% (31/122). Technical failure was strongly correlated with amputation at 30 days (P=0-001, r=0.29). Age and synthetic graft material were both associated with amputation during follow-up (P=0.008 and 0.043 respectively). When technical failure, patient age, graft material and adjunctive intervention were entered into a Cox regression model, technical failure (hazard ratio 2.58; 95% CI 1.09-6-08), age (HR 1.06, 95% CI 1.019-1.103) and synthetic graft material (HR 2.63; 95% CI 1-6.92) remained independent predictors of amputation during follow-up.

At one month, the mortality rate was 6.5% (8/123). When entering age, smoking, hypertension, presence of acute limb ischemia, major haemorrhage and major amputation in a Cox regression model, higher age (HR 1.050; 95% CI 1.017 – 1.084), presence of acute limb ischemia (HR 3.22; 95% CI 1.39 – 7.48) and major amputation (HR 2.63; 95% CI 1.41 – 4.90), remained independently associated with mortality.

Amputation-free survival

Figure 5 shows the crude Kaplan-Meier estimates of amputation-free survival for vein and synthetic bypasses. In a Cox regression model with age, hypertension, acute limb ischaemia and major haemorrhage as covariates, higher age (HR 1.06; 95% CI 1.03-1.09) and acute limb ischaemia (HR 2.4; 95% CI 1.26-4.56) remained independent negative predictors of amputation-free survival.

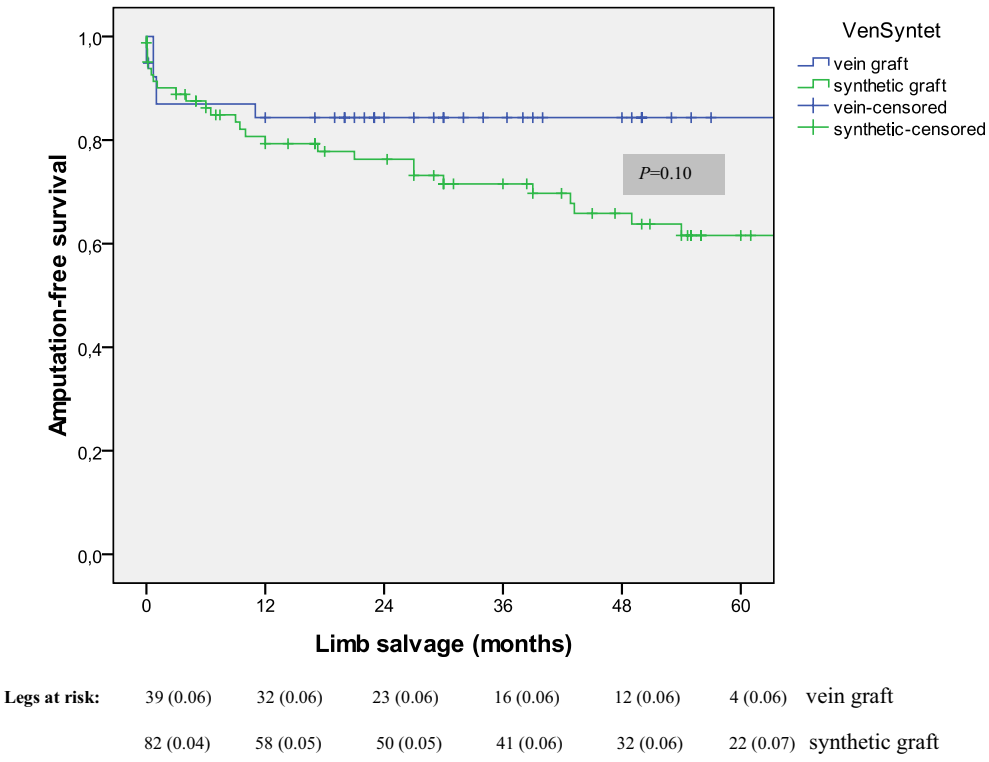

Figure 5: *Kaplan-Meier estimates of amputation-free survival after thrombolysis*

Discussion

This cohort is one of the largest reported series of patients undergoing thrombolysis for bypass graft occlusion. The rates of amputation and technical success were similar to those of other contemporary series of thrombolysis for lower limb ischaemia.[75, 76] When analysing factors associated with adverse outcomes, some findings were rather surprising. The association between ischaemic heart disease and technical success was possibly due to a statistical type I error related to a small sample size and the characteristics of the cohort (older individuals with multiple cardiovascular comorbidities), and did not appear to be caused by group differences in antithrombotic medication or graft type.

Less surprising was the association between technical failure of thrombolysis and synthetic graft material and amputation. The fact that an increased severity of limb ischaemia on presentation, age and major amputation were associated with mortality was equally unsurprising. A higher degree of ischaemia may negatively affect outcomes by increasing the risk of reperfusion injury and by increasing the risk of complications during treatment, and it may also be a surrogate marker for more advanced vascular disease, which in itself is associated with mortality.
The rate of intracerebral bleeding and major haemorrhage in this study is in line with existing literature.[34]

Most patients in this study underwent some form of adjunctive procedure, and this may be partly caused by the ability to identify and correct any underlying culprit lesions. It has also previously been shown that thrombolysis gives a higher number of patent run-off vessels compared with open surgery.[75]

The role of graft material on treatment success and longer-term outcomes remains somewhat unclear. In this study, synthetic grafts had a slightly increased likelihood of immediate technical success, but in the longer term they exhibited an increased risk of amputation. It has been postulated that the latter finding may be due to factors such as an increased risk of graft infection, ligation of collateral arteries and a history of previous vascular surgery in the same limb.[77] The presence of a synthetic graft may also be a surrogate marker of inferior conditions for successful and durable vascular reconstruction, as a venous conduit is virtually always the preferred option if at all possible.

The role of post-thrombolysis anticoagulation in order to prevent repeat occurrences is also not completely clear. Some authors have advocated the use of coumadin therapy[78], but there is a paucity of evidence surrounding treatment strategies and duration.

Because of its retrospective nature, this study suffers from several limitations. It was not possible to ascertain accurately the duration of symptoms prior to thrombolysis which may have been important for the outcome analysis, given that thrombus age may influence the susceptibility to thrombolytic degradation. Moreover, a longer duration of thrombosis may negatively affect the vessel wall of native conduits, reducing the likelihood of restoration of patency. In addition, there was no standardised protocol for graft surveillance and subsequent radiological patency data was not generally available.

Nonetheless, this study has shown that thrombolysis is a viable alternative for the treatment of infrainguinal bypass graft occlusion with acceptable rates of technical success and amputation-free survival.

4.2 RESULTS AND DISCUSSION STUDY II

The purpose of Study II was to investigate if prior systemic thrombolysis (IVT) influenced outcomes after carotid endarterectomy (CEA) or carotid artery stenting (CAS) for the treatment of symptomatic carotid artery stenosis.

***Table 11*:** Demographics of the study cohort

	Thrombolysis cohort *N*=79	Non-thrombolysis cohort *N* =3919*	P
Median age (range)	71 (37-84)	73 (40-92)	**0.04**
Gender (M/F)	M 54/F 25 (68%;32%)	M 2631/ F 1288 (67%:33%)	0.83
Neurological presentation			
Minor stroke	46/79 (58%)	1344/3919 (34%)	**<0.00001**
Major stroke	33/79 (42%)	70/3919 (1.8%)	**<0.00001**
Current smoking	15/54 (28%)	759/3077 (25%)	0.60
Treated for hypertension	60/79 (76%)	2923/3650 (81%)	0.36
DM	21/79 (27%)	735/3650 (20%)	0.16
Heart disease	19/67 (28%)	1117/3583 (31%)	0.62
Previous stroke or TIA	24/79 (30%)	678/3698 (18%)	**0.007**
Antithrombotic medication			
Aspirin only	36/78 (46%)	*NA*	
Clopidogrel only	3/78 (4%)	*NA*	
Dipyridamole only	3/78 (4%)	*NA*	
Warfarin	1/78 (1.3%)	*NA*	

Patient characteristics

The study included 3,998 patients who had undergone CEA or CAS for symptomatic carotid artery stenosis during the study period. Of these, 79 had undergone prior IVT. *Table 11* shows the baseline characteristics of the study cohort.

All patients in the thrombolysis cohort underwent IVT with rt-PA within 360 minutes of the onset of stroke symptoms (median 150 min, range 40 to 360 minutes). The median NIHSS score before thrombolysis was 8 (range 2 to 25) and after lysis the median score was 3 (range 0 to 18).

Carotid surgery and stenting

CEA or CAS was undertaken at a median of 10 days after IVT (range 0 to 108 days). Three of the 79 patients underwent CEA less than 48 hours after IVT. Fifty-seven of 79 underwent CEA or CAS within two weeks of IVT. In the control cohort (n=3919) the median time to CEA or CAS after the sentinel symptom was nine days (0 to178 days).

The majority (n=54) of the study patients underwent conventional CEA, 17 underwent eversion endarterectomy and six underwent CAS.

Complications and follow-up

The rate of complications after CEA or CAS in the patients who had received IVT was similar to that seen in the control group who had not undergone thrombolysis. The 30-day death and stroke rate was 2.5% after IVT and 3.8% in the control group (P=0.79). *Table 12* summarises the frequencies and types of complications seen in the two cohorts, and *Table 13* shows the characteristics of the patients in the IVT group who had suffered complications.

***Table 12*:** Complications after CEA/CAS in the two cohorts

Complications	Thrombolysis cohort (n=79)	Non-thrombolysis cohort (n=3,919*)
Total number of complications†	5/79 (6.3%)	551/3626 (15%)
Minor stroke	2/79 (2.5%)	62/3626 (1.7%)
Major stroke	0	46/3626 (1.3%)
TIA	0	42/3626
Cerebral hemorrhage	0	27/3626
Cranial nerve injury	0	175/3626
Reoperation for surgical site bleeding	3/79 (3.8%)	119/3626 (3.3%)
Myocardial infarction	0	54/3626 (1.5%)
Death within 30 days‡	0	31/3626 (0.9%)

†P=0.03; Thrombolysis cohort vs. nonthrombolysis cohort.

‡Death not included in the total complication rate

***Table 13*:** Characteristics of patients suffering complications after IVT and CEA/CAS

Patient	Age	Sex	Complication type	Days from trombolysis	Indication	Type of surgery
1	64	M	Reoperation for bleeding	1	Minor stroke	Conventional CEA
2	81	M	Retinal infarction	3	Minor stroke	Conventional CEA
3	78	F	Reoperation for bleeding	4	Minor stroke	Conventional CEA
4	81	M	Minor stroke	5	Major stroke	Conventional CEA
5	83	F	Reoperation for bleeding	6	Minor stroke	Eversion CEA

Having undergone IVT did not influence the overall 30 day postoperative complication rate (P=0.072).

There was no association between the time from IVT to subsequent CEA/CAS (P=0.189), and patients undergoing CEA/CAS within two weeks of IVT were not more likely to suffer any complications (P=0.15).

Discussion

This population-based study did not show an increased rate of complications following CEA or CAS. At the time, it was the largest reported cohort of patients undergoing CEA/CAS after IVT, demonstrating the unique opportunity for analysis of a small but increasing cohort that is afforded by the national vascular surgery and stroke registries. The compound 30-day stroke and death rate of 2.5% in the IVT cohort was in line with that seen in the control cohort (3.8%). There were no haemorrhagic strokes seen in the IVT group.

Interestingly, all patients who suffered complications underwent CEA/CAS within one week of IVT (as can be seen in *Table 3*). It is unclear whether this was associated with IVT, or more generally related to the timing of carotid intervention after the qualifying event. As reported by Strömberg and colleagues[79], very early CEA may increase procedural risk with a death and stroke rate of 11.5% if surgery was undertaken within 48 hours of the neurological event. This fell sharply to 3.6% for those patients who were operated on after three days but within seven days.

No increase of bleeding-related complications was detected when comparing the IVT group with the control group (3.8% versus 3.3%; P=0.79). However, given the short half-life of rt-PA in plasma of five minutes[69], it is not clear whether rt-PA affects haemostasis in patients within the time-frame of CEA/CAS being offered. As a comparison, in patients undergoing coronary artery bypass grafting (CABG) after IVT with streptokinase for myocardial infarction, an increase in bleeding and requirement of blood products was seen in those patients whose surgical procedure was undertaken 12 hours or less after cessation of thrombolysis. As with rt-PA, SK induces a fibrinolytic state with consumption of fibrinogen, and the replenishment of fibrinogen stores may take up to 24 hours because of the rate of fibrinogen synthesis.[69]

This study suffers from several limitations, owing to its retrospective design and small study population. Data from the national registries was not complete, although previous validation studies have shown excellent external and internal validity.[80, 81]

The small number of patients having undergone prior IVT makes a type II statistical error more likely, and also makes it difficult to draw any conclusions regarding the role of CAS in this group of patients, as there were only six patients who were treated by this method.

However, this study has demonstrated that carotid surgery and stenting may be safely undertaken in patients having undergone IVT for stroke. Future studies should focus on timing of the carotid intervention after IVT and patient selection.

4.3 RESULTS AND DISCUSSION STUDY III

The aim of this study was to compare the outcomes of an 'endovascular first' approach with a 'surgery first' approach for treating the first episode of dialysis access thrombosis.

Patient and dialysis access characteristics

During the study period there were 131 patients presenting with 149 episodes of primary thrombosis of an AVF or an AVG. The mean age of the patients was 65 years (SD 12.8 years; range 31 to 89 years); 40% were female. *Table 14* summarises the characteristics of the study cohorts (thrombolysis and open surgery). There were no significant differences in characteristics except for a lower proportion of females in the thrombolysis group and an increase in diabetic nephropathy and nephrosclerosis in the same group compared with the open surgery group.

***Table 14*:** Patient characteristics

	Thrombectomy n=90	Thrombolysis n=41	Overall n=131	P
Age (Median, range)	65 (31-88)	65 (39-89)	65 (SD 12.8; median 65)	0.86
Women (%)	41 (46)	11 (24)	52 (40)	0.02**
DM (%)	29 (32)	22 (54)	51/131 (39)	0.09
Cardiac risk (%)	27 (30)	12 (29)	39/131 (30)	0.51
On-going smoking (%)	11 (12)	4 (10)	15/131 (12)	0.58
Previous stroke/TIA (%)	10 (11)	7 (17)	17/131 (13)	0.40
Renal pathology				
DM nephropathy (%)	22 (24)	18 (45)	40/131 (31)	0.04**
Polycystic kidney disease (%)	13 (14)	3 (7)	16/131 (12)	0.39
Glomerulonephritis (%)	22 (24)	4 (10)	26/131 (20)	0.06
Nephrosclerosis (%)	5 (6)	8 (20)	13/131 (10)	0.02**
Hypertensive nephropathy (%)	11 (12)	0	11/131 (8)	0.02**
Post nephrectomy (%)	4 (4)	0	4 /131(3)	0.31
Other (%)	13 (14)	8 (20)	21/131 (16)	0.45
Antithrombotic medication				
Single platelet antagonist (%)	22 (24)	13 (32)	35/131 (27)	0.40
Double platelet antagonist (%)	4 (4)	0	4/131 (3)	0.31
Low molecular weight heparin (%)	4 (4)	0	3/131 (3)	0.31
Anticoagulant drug (%)	15 (17)	6 (15)	21/131 (16)	1.0
None (%)	43 (48)	21 (51)	64/131 (49)	0.85
Unknown (%)	2 (2)	1 (2)	3/131 (2)	1.0

There were 149 episodes of dialysis access thrombosis, of which 107 were treated with open surgical thrombectomy and 42 with thrombolysis. *Table 15* shows the distribution of different access types across the treatment groups.

***Table 15*:** Access types in the study cohort

	Thrombectomy (n=107)	Thrombolysis (n=42)	P
Access anatomy	*N(%)*	*N (%)*	
Radio-cephalic	12 (11)	7 (17)	0.42
Brachio-cephalic	9 (8)	2 (5)	0.73
Loop graft	39 (36)	16 (38)	0.85
Other lower arm *	15 (14)	4 (10)	0.59
Other upper arm **	32 (30)	13 (31)	1.0
Access material			
Native vein	27 (25)	14 (33)	0.32
Synthetic	80 (75)	28 (67)	0.32

*E.g. straight forearm grafts

** E.g. straight grafts, brachio-basilic transpositions

The dialysis accesses were treated for thrombosis at a median of 6.5 months after initial creation with an interquartile range of 17 months. This did not differ significantly between the groups (P=0.23).

Technical success and adjunctive procedures

Technical success was achieved in 96 of 149 total cases (64%). The success rates were 66/107 (62%) in the open group and 31/42 (74%), which was not significantly different (P=0.18).

Adjunctive procedures at the time of the study intervention were used in 61% (n=65/107) of the patients in the open group and in 88% (n=37/42) in the thrombolysis group, which was significantly different (P=0.001). *Table 16* details the type of adjunctive procedures undertaken in conjunction with the study intervention. Some patients had more than one adjunctive intervention performed.

***Table 16*:** Adjunctive interventions

Type of adjunct	Thrombectomy (N=107)	Thrombolysis (N=42)
Balloon angioplasty	16	34
Open anastomotic revision	26	4
Open interposition grafting	15	1
Stent/stent graft	2	2
Change of graft limb	6	0
Unknown	2	0

As discussed in section 3.5, the outcome patency time was the *post-intervention primary assisted patency time*. Several patients therefore had assistive procedures performed to maintain their dialysis access after the initial thrombolysis or thrombectomy, and these are detailed in *Table 17*.

***Table 17*:** Subsequent assistive procedures after thrombolysis or thrombectomy

	First procedure (n=38)	Second procedure (n=15)	Third procedure (n=9)	Fourth procedure (n=2)
Balloon angioplasty	26	7	3	1
Anastomotic revision	6	0	2	1
Interposition grafting	4	2	1	0
Stenting	1	6	3	0
Diagnostic Angiography	1	0	0	0
Median time in months (range)	5 (0-27)	9 (2-32)	21 (5-40)	11 (7-14)

Complications

There were few adverse events observed in the study cohort. Four patients in the open surgical group developed a postoperative surgical-site infection, three of which could be treated with antibiotics. There were no cases of significant bleeding, myocardial infarction or stroke.

Access patency

Figure 6 shows the crude Kaplan-Meier patency curves for each of the treatment groups (defined in section 3.5).

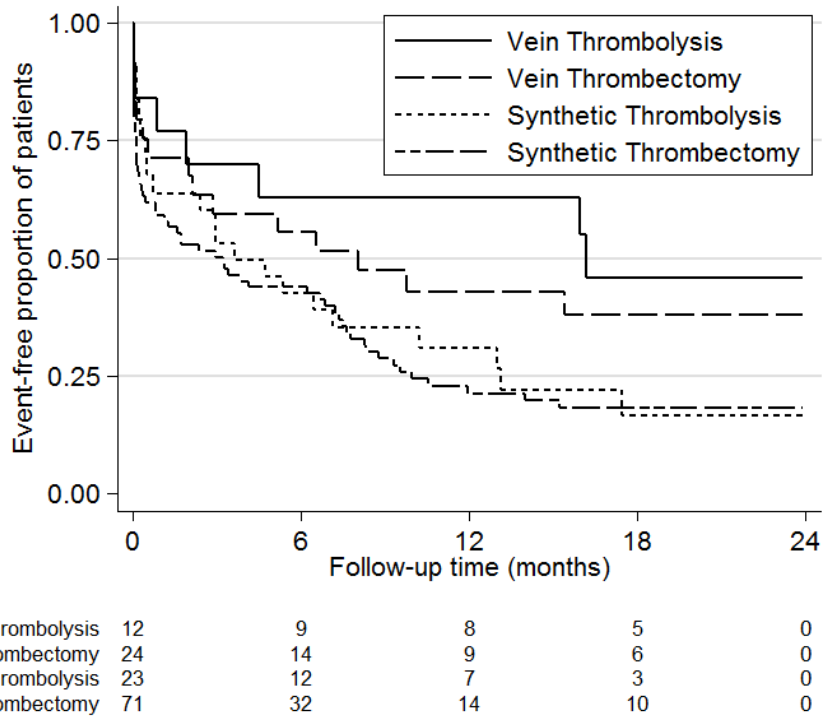

Figure 6: *Crude Kaplan-Meier curves of access patency*

The risk of rethrombosis was analysed over time following the study intervention. Patients were divided into four groups depending on type of treatment and access material as described in section 3.5. In order to provide a relevant comparison, the analysis was limited to those patients who had undergone an adjunctive intervention. *Figure 7* shows the modelled risk of reocclusion for each of the groups, and as indicated in *Figure 7*, the lowest risk was seen in AVFs after initial thrombolysis, followed by AVFs after open surgery and then AVGs undergoing thrombolysis. The highest risk of reocclusion was seen in AVGs after open surgery. The average risk increase between each treatment group was 41% (95% CI 0.4% to 98%) after correcting for sex, diabetes and fistula anatomy. *Figure 7* shows a graphical representation of the risk of rethrombosis per treatment group.

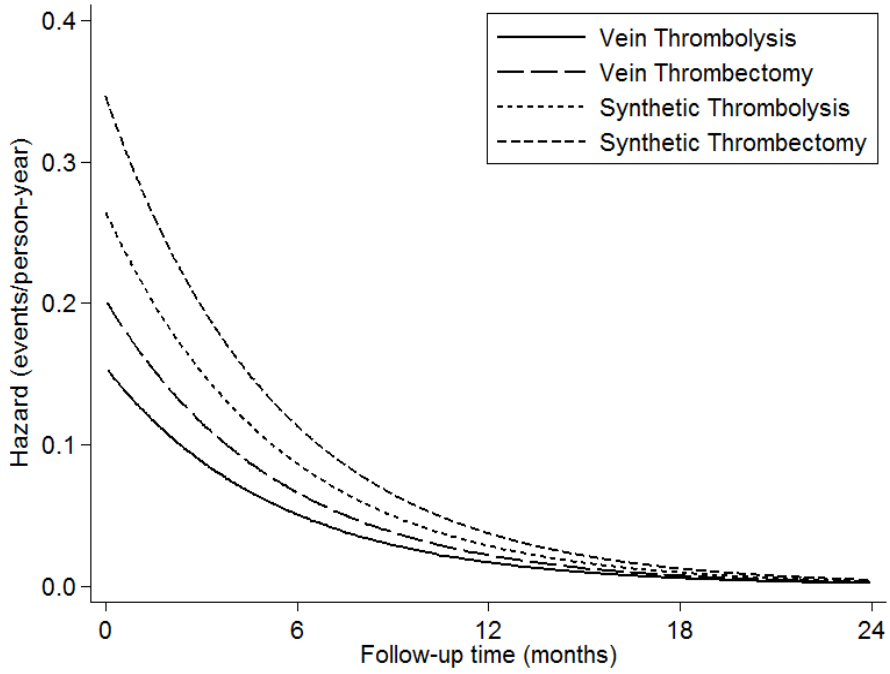

Figure 7: *Hazard curves for individual treatment groups. There is a 41% (0.41; 95% CI 0.4% to 98%) increase in risk for rethrombosis between each treatment group after adjusting for potential confounders*

Discussion

This study has demonstrated an improved patency after thrombolysis for both AVFs and AVGs. Unsurprisingly, more patients in the endovascular group underwent adjunctive procedures in conjunction with the initial thrombolytic treatment, which would have influenced the outcome. However, the difference between the groups remained even after limiting the analysis to those patients who had undergone such additional procedures, suggesting that thrombolysis does confer an advantage independent of the increased ability to visualise fistula anatomy and identify any underlying culprit lesions. Following on from the above, the patency was better overall for native fistulas compared with grafts, an outcome that has also been noted in other studies.[82, 83]

The complication frequency in this series was low, without any incidences of major haemorrhage. A contributing factor may have been that only the first episode of thrombosis for each AVF or AVG was studied. Increasing access usage with repeated puncture may possibly increase the risk of bleeding compared with a younger access that may not have been used prior to thrombosis. However, the study accesses were of varying ages and many had been used for a significant length of time, so it is not possible to attribute the low risk of bleeding observed solely to access age and usage in this series. Importantly, there was no significant difference in access age between the endovascular and open groups, which could have biased the outcome of the study.

One of the main limitations of this study is the absence of a formalised treatment protocol for dialysis access thrombosis at the participating centres. This could have influenced patient selection and makes the groups more heterogenous. Intraoperative angiography was not routinely performed, something which may have improved the outcomes seen in the thrombectomy group. It has previously been recommended that such imaging be routinely performed during open surgical procedures for access thrombosis.[84] Its retrospective nature and the way in which thrombolytic therapy is documented in the medical records made a robust calculation of the total dose administered of rt-PA impossible, which could have been a factor affecting the results. Unfortunately, the same reason made it impossible to record accurately the duration of access thrombosis prior to the study intervention, something which has been shown by Sadaghianloo and colleagues to influence outcomes, with improved results seen in very early thrombectomy.[85] Moreover, the number of patients was relatively small, which could have contributed to a statistical type II error.

Nonetheless, this study has showed an advantage of thrombolysis over open surgical thrombectomy for the treatment of thrombosis of both AVFs and AVGs, with an improvement in freedom from reocclusion that appears independent of any adjunctive procedures. Further studies should focus on the timing of treatment and the role of adjuncts such as pharmacomechanical thrombolysis in re-establishing access patency after thrombosis.

4.4 RESULTS AND DISCUSSION STUDY IV

This study aimed to investigate if and how the level of inpatient care during catheter-directed thrombolysis (CDT) affected safety-related outcomes. A secondary aim was to identify risk-factors associated with patient transfer to a higher level of care during CDT.

Patient characteristics and indications for thrombolysis

Two hundred and eighty-one episodes of CDT in 252 patients were recorded at the two participating centres during the study period (116 on the general vascular ward (Centre 1) and 136 on the postoperative recovery unit (Centre 2). *Table 18* shows a summary of the characteristics of the study population across the two centres.

***Table 18*:** Demographics of the study cohorts

	Centre 1 N=116	Centre 2 N=136	P
Female (%)	52 (45)	63 (46)	0.90
Age median (range)	73 (62)	69 (69)	0.13
DM (%)	44 (38)	37 (27)	0.08
Cardiac (%)	51 (44)	53 (39)	0.44
Cerebral (%)	16 (14)	17 (13)	0.85
Hypertension (%)	72 (62)	85 (63)	1.0
Renal insufficiency (%)**	15 (13)	12 (9)	0.21
Current smoking (%)	18 (16)	35(26)	0.03*
Indication (lower limb/dialysis access/upper limb)[§]	101/26/0	139/12/4	
Acute extremity ischemia (%)[§]	96 (76)	82 (82)	0.3
Antithrombotic medication[§] (%)			
Warfarin	16 (13)	16 (10)	0.57
Aspirin	64 (50)	86 (55)	0.55
Novel Oral Anticoagulant	0	3 (2)	0.26
Limb viability[§§] (%)			
Category I	95 (95)	108 (78)	<0.00001*
Category IIa	5 (5)	26 (19)	
Category IIb	0	5 (3.6)	
Iatrogenous embolization (%)[§]	24 (19)	5 (3)	<0.0001*

*P<0.05

**Excluding patients undergoing thrombolysis for dialysis access thrombosis

[§]All thrombolysis episodes (n=281)

[§§]Only thrombolysis for limb ischaemia (N=239)

The majority of patients underwent CDT for limb ischaemia (240/281 episodes; 85%). Two-hundred and twenty-three of 281 episodes (79%) were conducted for acute symptoms (<14 days' duration). It is noteworthy that iatrogenous embolisation during another endovascular procedure was significantly more common at Centre 1 than Centre 2.

Outcomes of thrombolysis

Overall success of CDT was achieved in 78% (218/281) of cases and the median duration of treatment was 20 hours with no difference between centres (P=0.89). Vascular access was most

often in the groin (238/281). Compartment syndrome after CDT for limb ischaemia was noted in 4.6% (11/240).

Bleeding and other complications

Bleeding of any severity was observed in 32% of patients (89/281). More patients on the general vascular ward had reported low-level bleeding (category 1 and 2) compared with those on the postoperative recovery unit (29/126 versus 14/155; P=0.002), but there was no difference in major bleeding (category 3 and above) between the groups (7/126 versus 3/155, P=0.12). *Table 19* details the types and frequencies of complications observed in the groups.

***Table 19*:** Complications of thrombolysis

	Centre 1 (N=126) (%)	Centre 2 (N=155) (%)	P
Conversion to open surgery/amputation	12 (9.5)	19 (12)	0.63
Acute myocardial infarction	3 (2.4)	3 (1.9)	1.0
Ischaemic stroke	1 (0.8)	2 (1.3)	1.0
Haemorrhagic stroke	0	2 (1.3)	0.5
Intractable pain	12 (9.5)	11 (7.3)	0.52
Severe confusion	6 (4.7)	4 (2.6)	0.34
Other			
Renal failure	2 (1.6)	6 (3.9)	0.3
Hospital-acquired pneumonia	2 (1.6)	2 (1.3)	1
Sepsis	1 (0.8)	3 (1.9)	0.63
GI bleeding	2 (1.6)	1 (0.6)	0.59
Hypofibrinogenaemia	1 (0.8)	2 (1.3)	1
Multi-organ failure	0	2 (1.3)	0.5
Death	1(0.8)	1(0.6)	1.0
Bleeding (%)			
Class 0	70 (56)	122 (79)	
Class 1	29 (23)	14 (9)	
Class 2	20 (16)	16 (10)	
Class 3a	7 (6)	3 (1.9)	
Compartment syndrome	5 (3.9)	6 (3.9)	0.76
Transfer to higher level of care (% of whole cohort)	17 (13)	7 (4.5)	0.01*
Confusion	6 /17(35)	0	
Other complication	4 /17(24)	7/7 (100)	
Lack of resources on ward	6/17 (35)	n/a	
Unknown	1/17 (6)	0	

There were no differences in the frequency of non-bleeding related complications between patients who had undergone CDT on the general vascular ward compared with those on the postoperative recovery unit. There were two haemorrhagic strokes (0.7%) in the cohort. Eleven per cent (31/281) of cases required conversion to open surgery or amputation during the same inpatient episode. There were two deaths in the cohort (one at each centre), relating to ischaemic stroke and multiorgan failure respectively.

Transfer to a higher level of care

In total, 24 patients were transferred to a higher level of care across both centres (8.5%).
Patients on the vascular ward were more likely to require transfer to a higher level of care during CDT than those on the postoperative recovery unit (P=0.001). *Table 20* displays the characteristics of the transfer patients compared with those who did not require transfer.

***Table 20*:** Characteristics of patients transferred to a higher level of care

	Transfer (N=18)	Non-transfer (N=257)	P
Age (mean, SD)	76±11	69±13	0.04*
Female (%)	13/18 (72)	117/257 (46)	0.03*
DM (%)	5/18 (28)	82/257 (32)	0.80
Duration of thrombolysis	22.1h	22.8h	0.68
Cardiac (%)	13/18 (72)	100/257 (39)	0.01*
Cerebral (%)	5/18 (28)	30/257 (12)	0.06
Hypertension (%)	11/18 (61)	160/257 (62)	1.0
Current smoking (%)	3/18 (17)	55/257 (21)	0.58
Indication (%)			
Limb ischaemia	16/18 (89)	218/257 (85)	1.0
Dialysis access	2/18 (11)	35/257 (14)	
Arm ischaemia	0	4/257 (1.6)	

The differences observed between the two groups were increasing age, a higher proportion of females and the presence of cardiac disease in the transfer cohort. When these variables were entered into a logistic regression model, cardiac disease remained as an independent risk factor for transfer (OR 3.2; 95% CI 1.04-9.8; P=0.04).

Discussion

To our knowledge, this is the only study that has directly examined the influence of patient level of care on the safety of CDT. In Sweden, most vascular surgical patients undergoing CDT are cared for on a high-dependency unit[86] and there is a paucity of evidence surrounding the subject.

In this study, no systematic differences were detected in patient characteristics between the two centres that may have themselves explained the observed outcomes. The frequency of bleeding and other complications was similar to previously reported numbers.[34, 76, 87]
A strength of this study is the joint treatment protocol for CDT that is employed by both participating centres. Moreover, the organisation of services is such that there is an overlap of

the vascular surgeons and interventional radiologists performing CDT at both hospitals, reducing the risk of bias.

The limitations of the study include its retrospective design and relatively small cohort (n=252), and the low frequency of the study end-points.

In conclusion, this study has shown that a lower level of care (general vascular ward) does not significantly increase the risk of adverse events during CDT for limb ischaemia and dialysis access thrombosis compared with a high-dependency unit, provided appropriate patient selection and adequate training of nursing staff. Future work should address the cost-benefit implications and logistical consequences of differing levels of care on the provision of CDT.

5 GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The works included in this thesis have examined different aspects of thrombolytic treatment in a large and diverse group of patients within the context of vascular surgery. The overall aim was to investigate the outcomes of thrombolytic treatment in some of the most commonly seen patient groups, and the resulting heterogeneity is reflective of the clinical questions facing vascular surgeons and interventional radiologists on a daily basis.

The huge increase in the popularity of endovascular methods for the treatment of peripheral vascular disease has brought significant advances in both techniques and materials, enabling the clinician to treat more patients in this way than ever before. An important advantage of the endovascular approach is reduced invasiveness, which also opens the possibility of treating patients who would otherwise not be offered vascular surgery.

Furthermore, the development of more rapid-acting and specific thrombolytic agents (with a reduced risk of unwanted remote bleeding) may also increase the clinical utility of thrombolysis and broaden the indications for its use. However, the 'ideal thrombolytic agent' is yet to be found.

The topics in this thesis concern clinical outcomes such as limb salvage and vascular/conduit patency (Study I and III), as well as safety-related end-points such as the development of complications (Study II and IV).

Retrospective analysis of data from national registries and medical records affords a relatively quick assessment of the parameters of interest, but will always be hampered by the quality of data input and the possibility of irreconstructible incompleteness of information. It is apparent from this and other studies that clinical end-points can be determined reasonably accurately from retrospective scrutiny of collected data, and that nationwide registries afford the researcher a unique opportunity to study smaller subgroups of patients or outcomes with low event-rates. However, this does not obscure the need for further prospective research into the questions posed by this thesis.

The role of CDT in the treatment of infrainguinal bypass graft occlusion was addressed in Study I, where acceptable limb-salvage rates were observed in the cohort. Although less invasive than open surgery, CDT can be a relatively time-consuming affair. This somewhat limits its applicability, as patients who have immediately threatened limbs (i.e. where the degree of ischaemia is so severe that there is a risk of limb loss unless the extremity is revascularised immediately) require quicker results than the method can afford. There have therefore been numerous attempts to develop adjuncts to CDT to enhance its effect and quicken its onset of action.

Based on the currently available evidence, rheolytic thrombectomy (RT), a form of pharmacomechanical thrombolysis, could be considered the most promising.[88] Rheolytic

thrombectomy can be used either as a stand-alone method for thrombus clearance or as an adjunct to CDT in order to debulk thrombus and thereby possibly reduce the time required to clear the thrombotic material. It can also be used for the delivery of thrombolytic agent via the PowerPulse method.[89]

In a very recent report by Leung and colleagues[90], the AngioJet® device was evaluated in the treatment of acute limb ischaemia in 283 patients in a multi-centre prospective observational study. Patients were treated with either RT only or with RT and CDT. Those who had undergone RT only exhibited higher rates of amputation-free survival compared with those who also underwent CDT (P=0.017). The RT-only group also had a significantly shorter procedure duration compared with the RT+CDT cohort (1.6h versus 23h; P<0.001). In this study there was a significant proportion (35%) of patients with immediately threatened limbs (Rutherford class IIb[91] and above), and these were more likely to undergo RT together with CDT, which may in part explain the observed difference in amputation-free survival.

The development of further methods to augment CDT may in a longer-term perspective enable the treatment of patients whose limbs would otherwise not be salvageable using traditional CDT only, and where open surgery may not be possible.

The small but increasing group of patients being treated with IVT before carotid intervention for stenosis of the carotid artery is also an example of the need for further large, multi-centre prospective registries to enable more robust analysis of the outcomes. At the time of publication, Study II was the largest reported series with 79 patients. Subsequently, a Nordic collaboration published the results of a retrospective registry study of 202 patients who underwent CEA after IVT (in which the majority of patients from Study II were included).[43] Of these, only 117 had undergone CEA within 14 days of their qualifying neurological event, and similar to the findings in Study II in this thesis, these authors did not demonstrate an increase in adverse events in the IVT patients. However, this study suffered from significant gaps in data owing to its retrospective design and the constraints imposed by the amount of information collected in each of the participating registries, which somewhat limits the conclusions that can be drawn from the report.

Taken together, the available evidence points to the conclusion that IVT does not negatively influence the outcomes after CEA for symptomatic carotid artery stenosis. However, the evidence for timing of the procedure remains weak, and further prospective work should be done to quantify the risks associated with very early procedures.

The difficulty in assessing clinically relevant outcomes in a population reflective of that seen in everyday vascular surgery practice is highlighted by Study III, where there is a significant heterogeneity in many of the patient-related variables, as well as in the type of dialysis access studied. It also highlights the difficulties in determining a clinically useful measure of patency. In this study, a composite patency measure defined as the time between completion of surgery or thrombolysis and the next episode of clinically verified thrombosis was used. According to current reporting standards[73], this was the *post-intervention primary assisted patency*.

It is possible to divide the patency time into several subsegments based on any further interventions that are done to maintain fistula function. However, although this may be a more stringent method, it complicates the survival analysis and may be less clinically relevant, as it is the next episode of thrombosis that has the biggest impact on patient care. Moreover, there was no consistently available data on access surveillance. Many authors[51, 92] have used the Transonic® ultrasound dilution method for interim surveillance of AVF/AVG function, and such measurements often guide clinical decision-making concerning the need for assistive procedures such as balloon angioplasty or open revision of the access.

Nonetheless, Study III does demonstrate the potential for improved outcomes using an endovascular-first approach, although more research into the role of newer adjuncts such as drug-eluting balloons, augmented systemic anticoagulation and platelet inhibition is required, as well as further development of hybrid (combined open and endovascular) techniques in dialysis access management.

The role of inpatient care during thrombolysis is an area which has not been studied extensively, despite the increasing popularity of catheter-based techniques, and to date there have been no published studies of the influence of patient monitoring on adverse outcomes during CDT. This thesis has demonstrated that, given adequate training of nursing staff and patient selection, a regular vascular ward can provide safe care for patients undergoing CDT both for limb ischaemia and dialysis access occlusion. Patients with significant comorbidity (in particular cardiac disease), advancing age and possibly also women are however more likely to require a higher level of care, which demonstrates the importance of careful patient selection.

The findings in this study could have an impact on the utilisation of healthcare resources, simplifying logistics surrounding patient care and may lead to reduced costs. In a recent study of the cost-effectiveness of an endovascular (CDT) versus an open surgical approach for the treatment of acute limb ischaemia, Lurie and colleagues[93] found that the costs associated with endovascular treatment by far exceeded those associated with open surgery ($34,800 versus $10,677). The increase in costs for CDT in this study was attributable in part to higher intensive care unit costs in this group. These findings underline the importance of re-evaluating existing treatment protocols in order to ensure the best utilisation of available resources while maintaining the highest level of patient safety.

Taken together, the results of the studies included in this thesis show that thrombolysis is a safe and efficacious treatment in many contexts within vascular surgery. There is nonetheless a need for more prospective research into the safety and outcomes of endovascular treatment methods in this large group of patients, especially considering the very fast development of techniques and devices. This also poses questions to clinicians regarding resource utilisation, and it is important that the costs of these new methods are adequately analysed upon implementation in a public healthcare system.

The role of pharmacomechanical thrombolysis also needs to be further evaluated, especially in the context of offering endovascular treatment for severe acute limb ischaemia in cases where open surgery may not be possible.

Furthermore, the question of how to ensure optimum results after successful re-establishment of vascular patency remains, and further research should be aimed at investigating the role of adjunctive medical treatment after thrombolysis.

6 CONCLUSIONS

- Catheter-directed thrombolysis for the treatment of acute infrainguinal bypass graft occlusion results in good amputation-free survival with relatively few serious complications. Synthetic bypasses exhibit a slightly higher immediate technical success rate, but in the longer term, native grafts tend to do better.

- The administration of intravenous thrombolysis does not seem to cause an increase in adverse events and complications seen after CEA or CAS in patients with symptomatic carotid artery stenosis, although the risk of very early procedures (within three days of the qualifying neurological event) needs further evaluation.

- Compared with open surgery, CDT of a native or prosthetic dialysis access yields a lower risk of rethrombosis even when removing the influence of adjunctive procedures. Autologous fistulas appear to fare better than prosthetic grafts after both open surgery and thrombolysis.

- When evaluating safety-related outcomes of CDT in patients with limb ischaemia or dialysis access occlusion, a lower level of care as provided on a general vascular ward was not associated with an increase in adverse events compared with the higher level of care provided on a postoperative recovery unit wth continuous monitoring of physiological parameters. Cardiac disease was an independent risk factor for transfer to a higher level of care, and age and female gender may also increase the likelihood of transfer. These findings could help in selecting appropriate patients for CDT and may have an implication for healthcare-associated costs and resource utilisation.

7 SAMMANFATTNING PÅ SVENSKA

Användning av propplösande läkemedel, s.k. trombolys har under de senaste 20 åren blivit mycket vanligt i behandlingen av patienter med plötsligt cirkulationsbortfall i ben eller arm, stroke, hjärtinfarkt eller djup ventrombos. Denna typ av behandling kan ges antingen ospecifikt in i blodet som vidare transporterar den propplösande substansen till det drabbade kärlet (intravenös trombolys) eller via en kateter direkt in i själva blodproppen (kateterledd trombolys). Dessa behandlingsmetoder har visat sig minska risken för bestående men hos patienter med stroke. När det gäller intraarteriell kateterledd trombolys innebär detta vanligen en skonsammare metod för patienten som om behandlingen lyckas inte behöver genomgå ett större kirurgiskt ingrepp på sitt ben eller arm för att återställa cirkulationen.

Syftet med denna avhandling var att se hur trombolys påverkar utfallet hos olika grupper av patienter med kärlsjukdom. Mer specifikt undersöktes (I) hur utfallet efter propp i kärlgraft i benen påverkades av trombolysbehandling, (II) om trombolysbehandling för stroke ökade risken för komplikationer hos patienter som sedermera behandlades med operation av halspulsådern p.g.a. åderförkalkning, (III) hur det går för patienter som drabbas av stopp i fistlar för dialysbehandling p.g.a. njursvikt som behandlas antingen med sedvanlig operation eller kateterledd trombolys och slutligen (IV) vilken roll vårdavdelningen på sjukhus spelar för de patienter som genomgår intraarteriell trombolysbehandling för blodpropp i benen eller stopp i dialysfistlar. Generellt har patienter som genomgår sådan behandling vårdats på en intensivvårdsavdelning eller en intermediärvårdsavdelning som har en högre personaltäthet och mer övervakning av fysiologiska parametrar som t.ex. blodtryck och puls.

Man kan dela upp studierna i två generella grupper: Studier av det kliniska resultatet av trombolysbehandling avseende behandlingsframgång och risk för återfall (I och III) samt studier av säkerheten av trombolysbehandling avseende komplikationer hos patienterna (II och IV).

Studie I visar att trombolys gav ett bra resultat avseende behandlingsframgång, i över 80 % av fallen gick det att lösa upp proppen i kärlgraftet på benet. Risken för amputation av det drabbade benet var låg både efter en månads och ett års uppföljning. Äldre patienter och patienter där det inte gick att lösa proppen hade en högre risk för amputation och död.

I studie III innebar trombolys en lägre risk för nytt stopp i dialysfistlar jämfört med om patienten hade genomgåtten vanlig operation. Fistlar gjorda av konstgjort material hade sämre behandlingsframgång och en ökad risk för nytt fistelstopp.

Studie II visade att föregående trombolys inte gav någon ökad risk för komplikationer hos patienter som genomgår operation av halspulsådern p.g.a. åderförkalkning och slaganfall (stroke). Risken för död eller stroke efter operation var 2.5% i gruppen som hade behandlats med trombolys jämfört med 3.8% för patienter som inte hade behandlats med trombolys men genomgått samma typ av operation.

Studie III visade att vård på en vanlig vårdavdelning för kärlkirurgi inte gav någon ökad risk för komplikationer under pågående intraarteriell kateterledd trombolys jämfört med vård på en avdelning med en högre grad av övervakning av patienterna och med högre personaltäthet. Andelen av komplikationer som blödning, hjärtinfarkt och stroke var samma hos båda grupperna.

Sammanfattningsvis påvisar resultaten i denna avhandling att trombolys är en säker behandlingsmetod som ger goda resultat avseende behandlingseffektivitet och risk för återfall av blodpropp i det behandlade kärlet. Att vårda selekterade patienter på en vanlig kärlkirurgisk avdelning under trombolysbehandling är inte förknippat med ökad risk för komplikationer vilket kan ha en stor betydelse för resursfördelning inom vården samt vårdkostnader.

8 ACKNOWLEDGEMENTS

Rome was not built in a day and neither was this thesis…It has taken rather a long time to finish this work and it certainly has been a collaborative effort, both on a personal and a professional plane. I would in particular like to extend my sincere thanks to the good people listed below. If you cannot see your name and you think you should be there, do not fret – I will make it up to you in some other way!

Firstly, I would like to express my enormous gratitude to my main supervisor, **Carl-Magnus Wahlgren.** You have made all of this possible, and although we have had our discussions over the years, there has never been a time when I haven't thanked my lucky stars that I have such a good supervisor! It seems a long time ago since I was your first Ph.D. student, back in the days when your CV included 'Tennistränarutbildning steg II'. I'm looking forward to exploring some of the questions left unanswered in this thesis in the future, and I count on you to point me in the right direction!

Secondly, I would like to thank **Eric Wahlberg**, my co-supervisor. You made it possible for me to start my career in vascular surgery and you have always been there to give good advice during the years.

Thank you also **Ulf Hedin**, Head of the Department of Vascular Surgery, for creating such a good infrastructure for research within the department. The row of theses on the wall speak for themselves.

Gun Jörneskog, co-supervisor, thank you for being so friendly and helpful during the years. I'm sorry for leaving the diabetic path but it has been a pleasure nonetheless.

Karin Strigård, my external mentor, thank you for your generously hosted dinners in Stuvsta!

Stefan Acosta and **Monica Kuoppala**, thank you for such good collaboration during the making of Study I. Your patient cohort and input made it infinitely better.

Martin Björck, Thomas Troëng and **Björn Kragsterman**, thank you for your help with Study II. I'll probably never get another publication in such a fancy journal so I'm ever so grateful to you for making it possible.

Matteo Bottai, thank you very much for your excellent statistical guidance in Study III. Working with you has made it painfully obvious why I am not a professor of statistics.

Thank you to all my colleagues (past and present) at the Department for Vascular Surgery at Karolinska University Hospital: **Alireza, Anton, Claes, David, Esther, Eva, Göran, Hedvig, JanE, Joy, Lena, Linus, Maria, Marianne, Mette, Olga, Ove, Peter, Rebecka,**

Staffan, Ulrika and **Ylva**. A special mention goes to **Calle M** and **Maggie** for helping out with Study IV, much appreciated!

Thank you also **Tina** for being such a good roommate at several points during the years. Have fun and kick ass in the world of upper GI surgery!

A big thank you to the whole **C14 team** for creating such a friendly working environment and for looking after the patients so well! A special thank you to **Maria A** for making the hours spent on 'Markörbaserad Journalgranskning' a pleasure!

Pär Olofsson, I will always be grateful for you believing in me back in 2007. I still miss your open door and the ability to phone 'Röris i Sumpan' any time for advice!

I would also like to extend a special thank you to **Nisse** and **Björne**, you were great mentors to me before you retired and it's a pleasure seeing you outside the confines of the hospital!

I'd also like to thank my colleagues at Södersjukhuset: **Anneli, Bengt, Bertil, Christian, Claes, Fredrik, Johnny, Magnus, Martin B, Martin D, Niklas** and **Sayid** for good on-calls and other collaboration during the years. Special thanks go out to **Mateusz** and **Peter** for help with Study III and IV, and to **Jonas** for always being supportive and encouraging during the years. I just wish I could be as good with SPSS as you!

Siw Frebelius, **Ann-Britt Wikström** and **Eva Oldenburg,** thank you for ensuring I don't create more administrative chaos than I already do and thank you for your eternal patience!

Thank you to **Martin Hughes** for putting me on the right track already at medical school (and you're right, I would have made a terrible GP…).

Pär Westlund, **Marina Dadaian**, **Anneli Stavréus-Evers** and the rest of the Reproductive Endocrinology lab, thank you for introducing me to the art of research and thank you **Elias Arnér** for making it possible in the first place through the KI Biomedical summer research school.

Thanks to the friendly people at the **Department of Surgery at Ersta Hospital**, the nine months I spent with you are still some of the best times I've had work-wise!

To **all my friends**, none mentioned and none forgotten. A huge thank you for all the lunches, dinners, drinks, travels, shopping, concerts, cycling, skiing and general fun things that have kept me sane during the years. I am a happier person with you guys around!

To **my family**, thank you for making me who I am today, for always being there and for always making sure I still have both feet firmly on the ground. I apologise for being a bit out of the loop but hopefully this will improve from now on!

And finally to **Nick**, you make me a better person and I am so very grateful for everything we have shared during the years.

9 REFERENCES

1. Tillett WS, Sherry S. The effect in patients of streptococcal fibrinolysin and streptococcal desoxyribonuclease on fibrinous, purulent, and sanguinous pleural exudations. J Clin Invest. 1949; **28**(1): 173-90.

2. Dotter CT, Rosch J, Seaman AJ. Selective clot lysis with low-dose streptokinase. Radiology. 1974; **111**(1): 31-7.

3. Rutherford RB. Vascular surgery. 6th ed. Philadelphia: Saunders; 2005.

4. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008; **359**(9): 938-49.

5. Versteeg HH, Heemskerk JW, Levi M, Reitsma PH. New fundamentals in hemostasis. Physiol Rev. 2013; **93**(1): 327-58.

6. Silvain J, Collet JP, Nagaswami C, Beygui F, Edmondson KE, Bellemain-Appaix A, et al. Composition of coronary thrombus in acute myocardial infarction. J Am Coll Cardiol. 2011; **57**(12): 1359-67.

7. Mullertz S, Clemmensen I. The primary inhibitor of plasmin in human plasma. Biochem J. 1976; **159**(3): 545-53.

8. Banerjee A CY, Banerjee UC. Streptokinase - a clinically useful thrombolytic agent. Biotechnology Advances. 2003; **22**: 287-307.

9. Garner R, Tillett W. Biochemical studies on the fibrinolytic activity of hemolytic streptococci. Journal of Experimental Medicine. 1934; **60**(2): 239-54.

10. Kaplan M. Nature and role of lytic factor in hemolytic streptococcal fibrinloysis. Proceedings of the Society for Experimental Biology and Medicine. 1944; **57**: 40-3.

11. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med. 1985; **312**(14): 932-6.

12. Ferguson LJ, Faris I, Robertson A, Lloyd JV, Miller JH. Intra-arterial streptokinase therapy to relieve acute limb ischemia. J Vasc Surg. 1986; **4**(3): 205-10.

13. White WF, Barlow GH, Mozen MM. The isolation and characterization of plasminogen activators (urokinase) from human urine. Biochemistry. 1966; **5**(7): 2160-9.

14. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. Ann Surg. 1994; **220**(3): 251-66; discussion 66-8.

15. Pennica D, Holmes WE, Kohr WJ, Harkins RN, Vehar GA, Ward CA, et al. Cloning and expression of human tissue-type plasminogen activator cDNA in E. coli. Nature. 1983; **301**(5897): 214-21.

16. Marder VJ. Historical perspective and future direction of thrombolysis research: the re-discovery of plasmin. J Thromb Haemost. 2011; **9 Suppl 1**: 364-73.

17. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med. 1993; **329**(10): 673-82.

18. Smalling RW. A fresh look at the molecular pharmacology of plasminogen activators: from theory to test tube to clinical outcomes. Am J Health Syst Pharm. 1997; **54 Suppl 1**: S17-22.

19. Van de Werf FJ. The ideal fibrinolytic: can drug design improve clinical results? Eur Heart J. 1999; **20**(20): 1452-8.

20. Melandri G, Vagnarelli F, Calabrese D, Semprini F, Nanni S, Branzi A. Review of tenecteplase (TNKase) in the treatment of acute myocardial infarction. Vasc Health Risk Manag. 2009; **5**: 249-56.

21. Hull JE, Hull MK, Urso JA, Park HA. Tenecteplase in acute lower-leg ischemia: efficacy, dose, and adverse events. J Vasc Interv Radiol. 2006; **17**(4): 629-36.

22. A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. N Engl J Med. 1997; **337**(16): 1118-23.

23. Gurewich V, Pannell R, Louie S, Kelley P, Suddith RL, Greenlee R. Effective and fibrin-specific clot lysis by a zymogen precursor form of urokinase (pro-urokinase). A study in vitro and in two animal species. J Clin Invest. 1984; **73**(6): 1731-9.

24. Weaver WD, Hartmann JR, Anderson JL, Reddy PS, Sobolski JC, Sasahara AA. New recombinant glycosylated prourokinase for treatment of patients with acute myocardial infarction. Prourokinase Study Group. J Am Coll Cardiol. 1994; **24**(5): 1242-8.

25. Ouriel K, Kandarpa K, Schuerr DM, Hultquist M, Hodkinson G, Wallin B. Prourokinase versus urokinase for recanalization of peripheral occlusions, safety and efficacy: the PURPOSE trial. Journal of vascular and interventional radiology : JVIR. 1999; **10**(8): 1083-91.

26. Toombs CF. Alfimeprase: pharmacology of a novel fibrinolytic metalloproteinase for thrombolysis. Haemostasis. 2001; **31**(3-6): 141-7.

27. Han SM, Weaver FA, Comerota AJ, Perler BA, Joing M. Efficacy and safety of alfimeprase in patients with acute peripheral arterial occlusion (PAO). J Vasc Surg. 2010; **51**(3): 600-9.

28. Comerota AJ. Development of catheter-directed intrathrombus thrombolysis with plasmin for the treatment of acute lower extremity arterial occlusion. Thromb Res. 2008; **122 Suppl 3**: S20-6.

29. Kessel DO, Berridge DC, Robertson I. Infusion techniques for peripheral arterial thrombolysis. Cochrane Database Syst Rev. 2004; (1): CD000985.

30. Ouriel K, Shortell CK, DeWeese JA, Green RM, Francis CW, Azodo MV, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. J Vasc Surg. 1994; **19**(6): 1021-30.

31. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. N Engl J Med. 1998; **338**(16): 1105-11.

32. Weaver FA, Comerota AJ, Youngblood M, Froehlich J, Hosking JD, Papanicolaou G. Surgical revascularization versus thrombolysis for nonembolic lower

extremity native artery occlusions: results of a prospective randomized trial. The STILE Investigators. Surgery versus Thrombolysis for Ischemia of the Lower Extremity. J Vasc Surg. 1996; **24**(4): 513-21; discussion 21-3.

33. Comerota AJ, Weaver FA, Hosking JD, Froehlich J, Folander H, Sussman B, et al. Results of a prospective, randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. Am J Surg. 1996; **172**(2): 105-12.

34. Berridge DC, Kessel DO, Robertson I. Surgery versus thrombolysis for initial management of acute limb ischaemia. Cochrane Database Syst Rev. 2013; **6**: CD002784.

35. Nilsson L, Albrechtsson U, Jonung T, Ribbe E, Thorvinger B, Thorne J, et al. Surgical treatment versus thrombolysis in acute arterial occlusion: a randomised controlled study. Eur J Vasc Surg. 1992; **6**(2): 189-93.

36. Ravn H, Bjorck M. Popliteal artery aneurysm with acute ischemia in 229 patients. Outcome after thrombolytic and surgical therapy. Eur J Vasc Endovasc Surg. 2007; **33**(6): 690-5.

37. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med. 1995; **333**(24): 1581-7.

38. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014; **384**(9958): 1929-35.

39. Annual report of the Swedish Stroke Registry (Riks-Stroke) 2014; 2015.

40. Gladstone DJ, Oh J, Fang J, Lindsay P, Tu JV, Silver FL, et al. Urgency of carotid endarterectomy for secondary stroke prevention: results from the Registry of the Canadian Stroke Network. Stroke. 2009; **40**(8): 2776-82.

41. Bartoli MA, Squarcioni C, Nicoli F, Magnan PE, Malikov S, Berger L, et al. Early carotid endarterectomy after intravenous thrombolysis for acute ischaemic stroke. Eur J Vasc Endovasc Surg. 2009; **37**(5): 512-8.

42. Crozier JE, Reid J, Welch GH, Muir KW, Stuart WP. Early carotid endarterectomy following thrombolysis in the hyperacute treatment of stroke. Br J Surg. 2011; **98**(2): 235-8.

43. Rathenborg LK, Venermo M, Troeng T, Jensen LP, Vikatmaa P, Wahlgren C, et al. Editor's choice - Safety of carotid endarterectomy after intravenous thrombolysis for acute ischaemic stroke: a case-controlled multicentre registry study. Eur J Vasc Endovasc Surg. 2014; **48**(6): 620-5.

44. Bazan HA, Zea N, Jennings B, Smith TA, Vidal G, Sternbergh WC, 3rd. Urgent carotid intervention is safe after thrombolysis for minor to moderate acute ischemic stroke. J Vasc Surg. 2015.

45. Mandavia R, Qureshi MI, Dharmarajah B, Head K, Davies AH. Safety of carotid intervention following thrombolysis in acute ischaemic stroke. Eur J Vasc Endovasc Surg. 2014; **48**(5): 505-12.

46. European Renal Care Providers Association Facts and Figures. 2015.

47. National Kidney Foundation Kidney Disease Outcomes and Quality Initiative (K/DOQI), 2006 update. . The National Kidney Foundation Inc. ; 2006.

48. Montagnana M, Meschi T, Borghi L, Lippi G. Thrombosis and occlusion of vascular access in hemodialyzed patients. Semin Thromb Hemost. 2011; **37**(8): 946-54.

49. Zeit RM, Cope C. Failed hemodialysis shunts. One year of experience with aggressive treatment. Radiology. 1985; **154**(2): 353-6.

50. Cynamon J, Lakritz PS, Wahl SI, Bakal CW, Sprayregen S. Hemodialysis graft declotting: description of the "lyse and wait" technique. Journal of vascular and interventional radiology : JVIR. 1997; **8**(5): 825-9.

51. Rajan DK, Clark TW, Simons ME, Kachura JR, Sniderman K. Procedural success and patency after percutaneous treatment of thrombosed autogenous arteriovenous dialysis fistulas. Journal of vascular and interventional radiology : JVIR. 2002; **13**(12): 1211-8.

52. Bittl JA, Cohen DJ, Seek MM, Feldman RL. Economic analysis of angiography and preemptive angioplasty to prevent hemodialysis-access thrombosis. Catheter Cardiovasc Interv. 2010; **75**(1): 14-21.

53. Crikis S, Lee D, Brooks M, Power DA, Ierino FL, Levidiotis V. Predictors of early dialysis vascular-access failure after thrombolysis. Am J Nephrol. 2008; **28**(2): 181-9.

54. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. Cochrane Database Syst Rev. 2014; **1**: CD002783.

55. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; **141**(2 Suppl): e419S-94S.

56. Hao Q, Dong BR, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev. 2015; **9**: CD004437.

57. Avgerinos ED, Chaer RA. Catheter-directed interventions for acute pulmonary embolism. J Vasc Surg. 2015; **61**(2): 559-65.

58. Bernardi E, Pesavento R, Prandoni P. Upper extremity deep venous thrombosis. Semin Thromb Hemost. 2006; **32**(7): 729-36.

59. Spiezia L, Simioni P. Upper extremity deep vein thrombosis. Intern Emerg Med. 2010; **5**(2): 103-9.

60. Semba CP, Deitcher SR, Li X, Resnansky L, Tu T, McCluskey ER. Treatment of occluded central venous catheters with alteplase: results in 1,064 patients. Journal of vascular and interventional radiology : JVIR. 2002; **13**(12): 1199-205.

61. Kasirajan K, Ouriel K. Current options in the diagnosis and management of acute limb ischemia. Prog Cardiovasc Nurs. 2002; **17**(1): 26-34.

62. Jeyabalan G, Saba S, Baril DT, Makaroun MS, Chaer RA. Bradyarrhythmias during rheolytic pharmacomechanical thrombectomy for deep vein thrombosis. J Endovasc Ther. 2010; **17**(3): 416-22.

63. Zhu DW. The potential mechanisms of bradyarrhythmias associated with AngioJet thrombectomy. J Invasive Cardiol. 2008; **20**(8 Suppl A): 2A-4A.

64. Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. Br J Anaesth. 2001; **86**(6): 859-68.

65. Uflacker R, Rajagopalan PR, Selby JB, Hannegan C. Thrombosed dialysis access grafts: randomized comparison of the Amplatz thrombectomy device and surgical thromboembolectomy. Eur Radiol. 2004; **14**(11): 2009-14.

66. Byrne RM, Taha AG, Avgerinos E, Marone LK, Makaroun MS, Chaer RA. Contemporary outcomes of endovascular interventions for acute limb ischemia. J Vasc Surg. 2014; **59**(4): 988-95.

67. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation. 2007; **115**(20): e478-534.

68. Jauch EC, Saver JL, Adams HP, Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013; **44**(3): 870-947.

69. Marder VJ. Thrombolytic Therapy. In: Kitchens CS, Konkle, B.A., Kessler, C.M. , editor. Consultative Hemostasis and Thrombosis: Elsevier; 2013. p. 526-37.

70. Clauss A. [Rapid physiological coagulation method in determination of fibrinogen]. Acta Haematol. 1957; **17**(4): 237-46.

71. Shafer KE, Santoro SA, Sobel BE, Jaffe AS. Monitoring activity of fibrinolytic agents. A therapeutic challenge. Am J Med. 1984; **76**(5): 879-86.

72. Nilsson CU, Tynngard N, Reinstrup P, Engstrom M. Monitoring fibrinolysis in whole blood by viscoelastic instruments: a comparison of ROTEM and ReoRox. Scand J Clin Lab Invest. 2013; **73**(6): 457-65.

73. Gray RJ, Sacks D, Martin LG, Trerotola SO. Reporting standards for percutaneous interventions in dialysis access. Technology Assessment Committee. Journal of vascular and interventional radiology : JVIR. 1999; **10**(10): 1405-15.

74. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; **123**(23): 2736-47.

75. Tiek J, Fourneau I, Daenens K, Nevelsteen A. The role of thrombolysis in acute infrainguinal bypass occlusion: a prospective nonrandomized controlled study. Ann Vasc Surg. 2009; **23**(2): 179-85.

76. Grip O, Kuoppala M, Acosta S, Wanhainen A, Akeson J, Bjorck M. Outcome and complications after intra-arterial thrombolysis for lower limb ischaemia with or without continuous heparin infusion. Br J Surg. 2014; **101**(9): 1105-12.

77. Nehler MR, Mueller RJ, McLafferty RB, Johnson SP, Nussbaum JD, Mattos MA, et al. Outcome of catheter-directed thrombolysis for lower extremity arterial bypass occlusion. J Vasc Surg. 2003; **37**(1): 72-8.

78. Brumberg RS, Back MR, Armstrong PA, Cuthbertson D, Shames ML, Johnson BL, et al. The relative importance of graft surveillance and warfarin therapy in infrainguinal prosthetic bypass failure. J Vasc Surg. 2007; **46**(6): 1160-6.

79. Stromberg S, Gelin J, Osterberg T, Bergstrom GM, Karlstrom L, Osterberg K. Very urgent carotid endarterectomy confers increased procedural risk. Stroke. 2012; **43**(5): 1331-5.

80. Stecksen A, Asplund K, Appelros P, Glader EL, Norrving B, Eriksson M. Thrombolytic therapy rates and stroke severity: an analysis of data from the Swedish stroke register (Riks-Stroke) 2007-2010. Stroke. 2012; **43**(2): 536-8.

81. Troeng T, Malmstedt J, Bjorck M. External validation of the Swedvasc registry: a first-time individual cross-matching with the unique personal identity number. Eur J Vasc Endovasc Surg. 2008; **36**(6): 705-12.

82. Huber TS, Carter JW, Carter RL, Seeger JM. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. J Vasc Surg. 2003; **38**(5): 1005-11.

83. Murad MH, Elamin MB, Sidawy AN, Malaga G, Rizvi AZ, Flynn DN, et al. Autogenous versus prosthetic vascular access for hemodialysis: a systematic review and meta-analysis. J Vasc Surg. 2008; **48**(5 Suppl): 34S-47S.

84. Bush RL, Lin PH, Lumsden AB. Management of thrombosed dialysis access: thrombectomy versus thrombolysis. Semin Vasc Surg. 2004; **17**(1): 32-9.

85. Sadaghianloo N, Jean-Baptiste E, Gaid H, Islam MS, Robino C, Declemy S, et al. Early surgical thrombectomy improves salvage of thrombosed vascular accesses. J Vasc Surg. 2014; **59**(5): 1377-84 e1-2.

86. Kuoppala M. Aspects on intra-arterial thrombolysis for lower limb ischemia. Malmö: Lund University; 2014.

87. Kuoppala M, Akeson J, Svensson P, Lindblad B, Franzen S, Acosta S. Risk factors for haemorrhage during local intra-arterial thrombolysis for lower limb ischaemia. J Thromb Thrombolysis. 2011; **31**(2): 226-32.

88. Ouriel K. A history of thrombolytic therapy. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2004; **11 Suppl 2**: II128-33.

89. Shammas NW, Dippel EJ, Shammas G, Gayton L, Coiner D, Jerin M. Dethrombosis of the lower extremity arteries using the power-pulse spray technique in patients with recent onset thrombotic occlusions: results of the DETHROMBOSIS Registry. J Endovasc Ther. 2008; **15**(5): 570-9.

90. Leung DA, Blitz LR, Nelson T, Amin A, Soukas PA, Nanjundappa A, et al. Rheolytic Pharmacomechanical Thrombectomy for the Management of Acute Limb Ischemia: Results From the PEARL Registry. J Endovasc Ther. 2015; **22**(4): 546-57.

91. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997; **26**(3): 517-38.

92. Rajan DK, Bunston S, Misra S, Pinto R, Lok CE. Dysfunctional autogenous hemodialysis fistulas: outcomes after angioplasty--are there clinical predictors of patency? Radiology. 2004; **232**(2): 508-15.

93. Lurie F, Vaidya V, Comerota AJ. Clinical outcomes and cost-effectiveness of initial treatment strategies for nonembolic acute limb ischemia in real-life clinical settings. J Vasc Surg. 2015; **61**(1): 138-46.